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Review

Hitting the 'mark': Interpreting lysine methylation in the context of active transcription ☆

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ABSTRACT

Histones and their posttranslational modifications (PTMs) play an important role in regulating DNA-templated processes. While some PTMs directly modulate chromatin architecture via charge effects, others rely on the action of reader or effector proteins that can recognize and bind the modification to fulfill distinct cellular outcomes. One PTM that has been well studied with regard to reader proteins is histone lysine methylation — a PTM linked to many DNA-templated processes including transcription, DNA replication and DNA repair. In this review, we summarize the current understanding of how histone lysine methylation is read during the process of active transcription. We also describe how the interpretation of lysine methylation fits into a larger, more complex 'code' of histone PTMs to modulate chromatin structure and function. These insights take into account emerging concepts in the field in an effort to help facilitate future studies. This article is part of a Special Issue entitled: Methylation Multifaceted Modification — Looking at Transcription and Beyond.

1. Introduction

Transcription involves the highly regulated recruitment of proteins and assembly of complexes at specific sites within the genome to facilitate the action of RNA polymerases. While many fundamental details of this process have been delineated, our understanding of how specificity for different genes is achieved remains an important question in modern biology. DNA sequence plays a fundamental role in this process by serving to bind sequence-specific transcription factors — however, this alone is insufficient to fully explain the differences found between the gene expression patterns observed across distinct cell types. A secondary component now realized to contribute to this specificity is chromatin.

While originally thought of as a passive barrier to the passage of RNA polymerase, a wealth of research has shown that chromatin (consisting of histone proteins wrapped by DNA into nucleosomes) plays both an active and dynamic role in the process of facilitating and repressing gene transcription [1–4]. Despite a near-ubiquitous presence throughout the genome, histones contribute to the specificity of transcription, at least in part, through their diverse array of post-translational modifications (PTMs). The continually expanding list of PTMs includes modifications such as acetylation, methylation, phosphorylation, ubiquitylation and sumoylation, as well as less characterized and defined modifications including ADP-ribosylation, citrullination, and glycosylation [5–8]. In addition to single modifications, PTMs can exist together in a multitude of potential combinations. Distinct combinations of PTMs have been shown to occur at specific regions of the genome depending on a number of factors including transcriptional activity [9]. Histone PTMs primarily function in transcription by serving as points of recognition for transcriptional regulators [5,8]. These regulators contain at least one, but in many cases, several highly conserved so-called effector or reader domains that are capable of distinguishing between, and binding to, specific modified or unmodified states of histone residues, or combinations of histone residues that are modified and/or unmodified [5,10–12]. Along with the increasing number of histone PTMs (and combinations thereof) that have been recently identified [13], the number of proteins that have been found to recognize specific histone modification states using conserved reader domains has also rapidly increased (see Table 1).

One of the most well characterized PTMs in transcription is lysine methylation [5,14]. Histone lysine methylation occurs primarily on histone H3 at lysines 4, 9, 14, 18, 23, 27, 36 and 79 and on histone

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Table 1
Reader domains that recognize transcription-associated lysine methylation.

Domain	Binding residues	Examples	References
PHD finger	H3K4	BPTF, ING2, TAF3	[22,36,64,65,103]
Chromo	H3K4	CHD1	[28,29]
	H3K36	Eaf3, MRG15, MSL3	[78–80,97,98,101]
Tudor	H3K4	Sgf29, JMJD2A	[40,41,53,54]
	H3K36	PHF1, PHF19	[89–92]
BAH	H3K79	Sir3	[115,116]
PWWP	H3K36	Ioc4, BRPF1	[85,86,95]
ADD	H3K4	DNMT3A/B	[58,59]
CW	H3K4	ASHH2	[137]

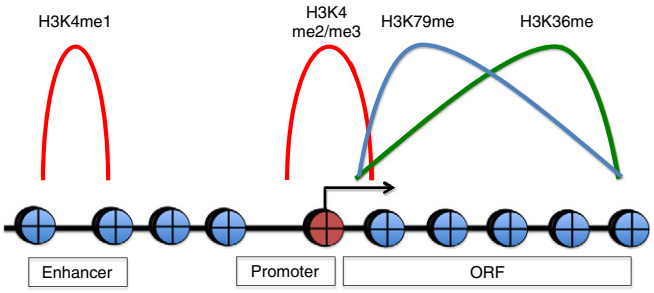

Fig. 1. Distribution of active methylation across genes. Histone lysine methylation exists in distinct patterns in and around actively transcribed genes. Shown is a representative model of a gene region with corresponding enrichment of indicated methylation state. Methylation enrichment reflects patterns observed in mammals. The +1 nucleosome is displayed in red at the transcription start site (arrow).

H4 at lysine 20 [6,14]. A number of these methylation events have been linked to transcriptional regulation, including those at H3 lysines 4, 36 and 79 (associated with active transcription) and those at H3 lysines 9 and 27 (associated with gene repression and heterochromatin formation) [3,5]. Unlike acetylation and phosphorylation, which in addition to recruiting proteins to chromatin can also directly affect chromatin structure by altering the charge of the histones, lysine methylation does not alter the charge of the residue and is therefore thought to primarily modulate chromatin structure through the recruitment of distinct reader proteins that possess the ability to facilitate transcriptional activation or repression [5,11,14]. Lysine residues can be modified with up to three methyl groups (mono-, di- and trimethylation) on the epsilon amine of the side-chain, and importantly, reader domains can distinguish between the different methyl states producing distinct functional outcomes [5,11,14]. These observations demonstrate the complexity and fine level of control that lysine methylation contributes to chromatin function and transcriptional regulation.

Given the wealth of knowledge on the function of histone lysine methylation and the readers that mediate their function, this review will focus on how lysine methylation is read during gene expression with a specific emphasis on active transcription. We will focus on the proteins whose recruitment depends on specific methylation states during transcription and describe how lysine methylation contributes to transcription in the context of the 'histone code'. Lastly we will discuss newly identified methyllysine binding domains as well as poorly understood histone interactions that are of particular interest for future studies.

2. Lysine methylation and transcription initiation — H3K4 methylation sets the stage

Transcription begins with the ordered recruitment and assembly of the general transcription factors as well as gene specific factors at promoters and enhancers to facilitate the binding of RNA polymerase. This process is highly regulated to ensure that genes are only expressed at the right place and time. Part of this regulation relies on histone PTMs including lysine methylation. At active promoter regions, trimethylation at lysine 4 of histone H3 (H3K4me3) is the prominent methyllysine species (Fig. 1) [15–19]. In budding yeast, where much work has been performed on elucidating the role of chromatin in transcription, a single SET domain-containing histone methyltransferase, Set1, catalyzes H3K4 methylation [20]. The presence of H3K4me3 at promoter regions is established through the interactions of the Set1-containing complex COMPASS both directly with chromatin (discussed below) and with components of the transcriptional apparatus including the polymerase associated factor (PAF) complex and the phosphorylated C-terminal domain of RNA polymerase II (RNAPII) [20]. Although Set1 is the sole H3K4 methyltransferase in yeast, humans contain multiple enzymes that are capable of methylating H3K4 including SET1A/B (found in mammalian COMPASS) and, to a lesser extent, the mixed lineage leukemia proteins MLL1-4 [20,21]. While each of these enzymes methylate H3K4 in humans, they each function in an apparent context-dependent manner to establish the observed patterns of mono-, di- and trimethylation [20]. The regulated recruitment and activity of H3K4 methyltransferases in both yeast and humans ultimately shape the H3K4 methylation landscape, to dictate localization of the effector proteins that modulate transcription.

H3K4me3 has been well-studied with regard to its ability to affect protein recruitment to chromatin and a number of highly conserved structural domains, in particular the PHD finger, have been identified that can bind this modification (see Table 1). In addition, H3K4 methylation exemplifies how a single PTM can mediate a diverse range of cellular outcomes (Fig. 2). How H3K4 methylation is read and contributes to gene regulation are explored below.

Beginning with the early genome-wide analysis of histone PTMs, one of the most striking observations was the presence of a defined peak of H3K4me3 at the transcriptional start site (+1 nucleosome) of many actively transcribed genes (Fig. 1) [17,18]. These analyses suggested an important role for this PTM in transcription initiation, yet it was not until pioneering mass spectrometry work from the Mann laboratory that a connection to general transcription was established. Using H3K4me3 histone peptides to immunoprecipitate complexes from nuclear extracts, Vermeulen et al. identified the general transcription factor TFIID as a complex that was directly associated with this histone PTM [22]. Further in vitro analysis revealed that the interaction with H3K4me3 is mediated by a PHD-finger of the subunit TAF3 (Fig. 2F). In cells, the PHD finger of TAF3 was shown to be important for the recruitment of TFIID at a subset of promoters enriched for H3K4me3, and for transcription of the corresponding genes [22,23]. In addition, these studies also found that the TAF3 interaction with H3K4me3 is also important for the assembly of the preinitiation complex at promoters [23,24]. Taken together, these observations provide important insight into how the specificity of TFIID recruitment to gene promoters is achieved. Previous work established that both DNA sequence and histone acetylation help facilitate TFIID recruitment through the TATA box binding subunit TBP and the double bromodomain-containing TAF1 subunit, respectively (Fig. 2F) [25,26]. Since not all genes contain a consensus TATA box, and given the fact that histone acetylation is not restricted to promoter regions, the readout of H3K4me3 by TAF3 may provide an additional mechanism to achieve specificity and control for general transcription.

In addition to recruiting the general transcription factors, H3K4me3 may also modulate transcription by mediating interactions with RNA polymerase associated proteins. Recent work in yeast demonstrated that a RNA polymerase binding protein called Bye1 also interacts with H3K4me3 through its PHD finger [27]. The impact of this interaction on gene transcription is not entirely clear, but links H3K4me3 directly to the transcription machinery.

Lysine methylation is important for the chromatin interaction of a number of other proteins during transcription initiation whose recruitment and function are often gene specific. Moreover, many of

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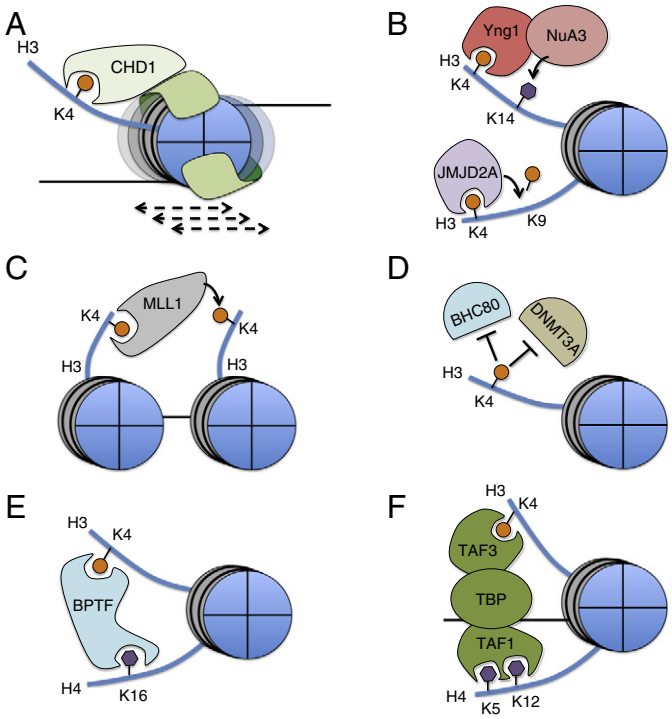

Fig. 2. Binding modes of methyllysine readers. Methyllysine can be read in multiple ways leading to distinct functional outcomes. Examples include recruitment and binding of chromatin remodeling complexes (A) or modifying enzymes (B, C), which can further modulate chromatin structure on the same or neighboring nucleosome. Lysine methylation can also repel proteins that would otherwise counteract the function of a given modification (D). Lastly, methyllysine functions in the context of other modifications to facilitate transcription. A single reader protein (E) or protein complex (F) can recognize multiple modifications at once, which confers specificity to chromatin binding. See text for further details.

these proteins or protein complexes posses chromatin-modifying activity, which, owing to that fact that lysine methylation cannot directly influence chromatin structure, is essential for methylation to mediate its effects on chromatin. One class of chromatin-modifying enzymes that read H3K4me3 is ATP-dependent chromatin remodelers (Fig. 2A). The first of these identified is human CHD1, which binds H3K4me3 through its tandem chromodomains [28,29]. Utilizing both in vitro reconstituted transcriptional assays as well as in vivo binding assays, CHD1 was shown to be recruited to chromatin via interaction with the mediator complex, but that H3K4me3 stabilized its chromatin interaction [30]. Aside from an ability to enhance chromatin binding and ultimately transcription, the downstream mechanisms facilitated by the CHD1–H3K4me3 interaction are not entirely clear; however, studies show that CHD1 plays a major role in the deposition of H3.3 implying that H3K4me3 may be linked to transcription-coupled histone variant deposition at gene promoters [31]. In addition to initiation, CHD1 has also been linked to transcription elongation events, indicating that H3K4me3 may function in several ways to aid in chromatin remodeling during the transcription cycle [32,33].

Another chromatin remodeling complex is the NURF complex, which interacts with H3K4me3 through the PHD finger-containing protein BPTF [34,35]. Initial studies showed that loss of H3K4me3 results in reduced binding of NURF to chromatin. Loss of H3K4me3 binding by BPTF in *Xenopus laevis* results in developmental defects thought to be due to the improper expression of key developmental genes including the *Hox* genes [35]. Recent studies indicate that as for TFIID, H3K4me3 binding by BPTF doesn't work alone, but rather in conjunction with H4K16 acetylation (Fig. 2E) [36]. The idea of a combinatorial readout of histone PTMs is discussed further below.

In addition to chromatin-remodeling activity, H3K4me3 can also recruit proteins with histone-modifying activity (Fig. 2B). The ability of one histone modification to regulate the outcome of others is termed 'cross-talk', and in some cases called '*trans*-tail' regulation when a PTM on one tail regulates the outcome of PTMs on other histone tails. One class of proteins with histone-modifying activity that H3K4me3 serves to recruit is histone acetyltransferases (HATs). HATs deposit acetyl moieties on lysine residues of histones and are typically associated with accessible chromatin and active transcription [5]. The first HAT complex identified to bind H3K4me3 is the yeast NuA3 complex, which acetylates the histone H3 N-terminal tail (Fig. 2B) [37]. Work from the Howe and Allis labs identified that the PHD-finger containing subunit Yng1 binds H3K4me3 and is required for the recruitment of the NuA3 complex to chromatin [38,39]. Furthermore they identified that H3K4me3 also promotes the acetyltransferase activity of the NuA3 complex. Impaired NuA3 recruitment and histone acetylation through the loss of Yng1 result in reduced expression of a subset of genes, likely due to a gene specific function of NuA3 in transcription. H3K4me3 was also identified to be important for the recruitment of another histone H3-specific acetyltransferase complex, the SAGA complex. Both human and yeast SAGA are able to bind H3K4me3 through the subunit Sgf29, which, unlike many readers of H3K4me3, facilitates binding through a tandem Tudor domain (TTD) [40,41]. Mutation of the TTD of Sgf29 in yeast results in a global decrease of H3 acetylation due to defective recruitment of SAGA [41]. Like loss of NuA3 recruitment, the inability of Sgf29 to bind histones alters the transcription of SAGA-dependent genes including those of the *GAL* family [41]. Lastly, the HBO1 acetyltransferase complex has been shown to bind H3K4me3 through the PHD finger-containing subunits ING4 and ING5 [42–44]. This interaction is important for transcription of select genes involved in apoptosis and the suppression of anchorage independent growth. In addition to its transcription role, HBO1 has also been shown to function in DNA replication [45,46], although it remains unclear if its function in this capacity is through H3K4me3 association. Collectively, the studies above linking histone acetylation with histone methylation at promoters provide a mechanistic link between these two modifications — a result further supported by studies showing that H3K4me3 is exclusively associated with multiply acetylated lysines on the H3 tail in cells [47,48].

Lysine methylation, especially at H3K4, can also serve to regulate itself as well as other sites of methylation. Interestingly, both the MLL and SET1A/B complexes have been shown to bind the modification that they catalyze (Fig. 2C). MLL1 contains a PHD finger that binds H3K4me3, while the SET1A/B interacting protein CFP1 serves the same function through its PHD finger [49–51]. The yeast Set1 complex, COMPASS, can also bind H3K4me3 through the PHD finger of Spp1 [52]. Loss of H3K4me3 binding by each of these complexes has been shown to result in diminished global levels of H3K4me3, suggesting a feed-forward mechanism where the presence of methylation is required for propagation of the mark on neighboring nucleosomes (Fig. 2C). H3K4me3 also promotes active transcription through the removal of repressive lysine methylation. A notable example of this is the histone demethylase JMJD2A, which binds H3K4me3 (in addition to H4K20me3) through tandem double Tudor domains (Fig. 2B) [53,54]. JMJD2A can remove trimethylation at lysines 9 and 36 of histone H3 (H3K9me3 and H3K36me3) with H3K9me3 serving as a modification associated with heterochromatin and inactive transcription [55,56].

Histone PTMs are not only read through direct interaction with a reader protein, but can also be refractory to reader protein binding (Fig. 2D). With this idea in mind, H3K4me3 can not only facilitate the recruitment of reader proteins, but can also prevent the occurrence of others (i.e., the association of repressive proteins) by directly interfering with their ability to interact with chromatin. An early example of this was observed with a subunit of the LSD1 lysine demethylase complex, BHC80, which removes methylation from H3K4. This protein

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contains a PHD finger, which preferentially binds unmethylated H3K4 [57]. Therefore, H3K4me3 can preserve itself by repelling a complex that would otherwise remove it. Another chromatin modification that is prevented by H3K4me3 is DNA methylation, which is commonly associated with transcription repression. Like BHC80, the DNA methyltransferases DNMT3A and DNMT3B bind to H3K4 in the unmethylated state through their ADD domains [58,59]. In vitro studies have shown that chromatin containing H3K4me3 nucleosomes are poor substrates for DNMT3A/B-mediated DNA methylation, which helps to explain the mutually exclusive pattern of DNA methylation and H3K4me3 genome-wide [59]. Finally, another example is with the NuRD repressor ATP-dependent remodeling complex, which was shown to associate selectively with histones unmethylated at H3K4 through the double PHD finger protein CHD4 [60–63]. These studies underscore the ability of a histone PTM to promote recruitment of factors that function to aid in transcriptional initiation, but at the same time, help to maintain an 'on' state by preventing association of 'off' machinery that would otherwise be inhibitory to gene transcription.

While H3K4me3 is often associated with active transcription, it is important to note that there are several examples where it serves to recruit repressive proteins. The first example of such recruitment was described for the PHD finger containing protein ING2 [64,65]. ING2 is a member of the mSin3a–HDAC1 histone deacetylase complex, which removes acetyl groups from lysine 14 of histone H3 — a modification associated with transcriptional activation [65,66]. ING2 is recruited to proliferation genes under cases of genotoxic stress to turn off transcription and aid in suppression of oncogenic growth [65]. Another apparent example of this is observed with the H3K4-specific histone methyltransferase MLL1. In a unique mechanism involving *cis–trans* proline isomerization, binding to H3K4me3 via its third PHD finger (MLL1-PHD3) may facilitate the recruitment of histone deacetylases to select genes and repress transcription [50,67]. Intriguingly, MLL1-PHD3 associates with HDAC1/2 following proline isomerization within MLL1 by the cyclophilin CyP33 [67]. Moreover, structural analysis found that MLL1-PHD3 can simultaneously bind H3K4me3 and CyP33 [50]. This is accompanied by work in vivo showing that CyP33 binding to MLL1 decreased histone acetylation at MLL1 target genes without affecting the ability of MLL1 to bind chromatin. Such a mechanism may serve as negative feedback to counteract the activating effects of H3K4 methylation.

Lastly and as mentioned above, lysine residues can be modified with up to three methyl groups and that these distinct methylation states have the capacity to direct unique cellular functions. Whereas H3K4me3 is associated with promoter regions, monomethylation (H3K4me1) is enriched (with other PTMs including H3K27 acetylation) at enhancer regions [68]. To date only one known reader protein has been described to specifically bind H3K4me1, which is the histone acetyltransferase Tip60 [69]. Binding of Tip60 to enhancers is important for proper gene expression, although the exact mechanism of action has yet to be elucidated (in large part due to the fact that Tip60 is found outside of enhancer regions as well [70]). Regardless, this observation further highlights the robust functionality of a single histone residue.

3. Gene body methylation — H3K36 and transcription elongation

While H3K4 methylation plays a role at promoter regions and enhancers, another site of lysine methylation is enriched in gene bodies — H3K36 methylation. Genome-wide analyses show that H3K36 methylation primarily exists with the lower methylation states (H3K36me1 and -me2) present near 5′ regions and higher methylation states (H3K36me2 and -me3) at the 3′ ends of genes (Fig. 1) [17,71]. As with other studies on histone lysine methylation, the understanding of H3K36 methylation developed initially in budding yeast where a single histone methyltransferase, Set2, catalyzes all three methylation events [72]. In metazoans, several enzymes can methylate H3K36 including, but not limited to NSD1-3 and SETD2 [73]. The role of H3K36 methylation is also quite diverse and has been shown to be involved in numerous functions including transcription, mRNA splicing, DNA replication and DNA repair [73,74]. However, the readers of H3K36 methylation, especially in the contexts of splicing, replication and repair are not as well defined as for H3K4 methylation. Discussed here are the readers of H3K36 methylation during transcription.

The function for H3K36 that has been most well defined is its role in transcription elongation. Early studies in yeast found genetic interaction between Set2 and H3K36 methylation with the transcription elongation machinery, and that Set2 physically interacts with the elongating form of RNAPII [32,75–77]. One of the well-understood functions of H3K36 methylation is to suppress transcription from 'cryptic' promoter sites occurring within the bodies of transcribed genes to ensure proper transcription from the primary promoter. In yeast, this mechanism occurs, in part, through the chromodomain-containing protein Eaf3 with the help of the PHD finger protein Rco1, which are members of the Rpd3S histone deacetylase complex [78–81]. In addition to a direct interaction with RNAPII, binding of Eaf3 to at least H3K36me2, in conjunction with Rco1 during transcription promotes the ability of Rpd3S to deacetylate histones in the wake of transcription [82–84]. This creates a more closed chromatin environment that prevents transcription from initiating within the gene body. Recent work has shown that the Isw1b chromatin-remodeling complex can also read H3K36 methylation through the PWWP domain-containing subunit Ioc4 [85,86]. Isw1b functions with Rpd3S to reestablish a closed chromatin state following transcription. More recent work indicates that Isw1b interacts with, and controls the spacing of, di-nucleosomes [87]. This function of Isw1b serves to stimulate Rpd3S activity, thereby providing a mechanism for how multiple chromatin-modifying complexes read H3K36 methylation [87].

In higher eukaryotes it appears that the same principle applies, but by a different set of mechanisms. Instead of directing histone deacetylation, H3K36 methylation recruits other repressive histone-modifying activities including lysine methylation and demethylation as well as DNA methylation. For example the H3K36 methyltransferase NSD3, which can bind H3K36 methylation via its PWWP domain, physically interacts with the H3K4 demethylase LSD2 [88]. Despite the removal of H3K4 methylation, the activity of the LSD2 complex in genes is required for proper transcription of target genes. H3K36 methylation can also promote the initiation and spread of histone methylation at lysine 27 in the coding regions through recruitment and binding of the Tudor domain-containing Polycomb repressive complex (PRC) subunits PHF1 and PHF19 [89–92]. This intriguing mechanism may play a role in the establishment of repressive domains within developmentally regulated genes that have been transcribed but become silenced. Lastly, the DNA methyltransferase DNMT3A, which also contains a PWWP domain, can bind H3K36 methylation, and this interaction is required for the full activity of the enzyme [93]. Taken together, the ability to create a repressive chromatin environment is a conserved feature of H3K36 methylation from yeast to humans, but multiple mechanisms are likely at play that may function in a context dependent manner.

Interestingly, and analogous to H3K4 methylation, H3K36 methylation also repels proteins from binding nucleosomes. This is the case for the histone chaperone Asf1. Within gene bodies, H3K36 methylation prevents Asf1 from performing its histone exchange function, which otherwise would lead to a less repressed chromatin environment [94]. It remains to be determined, however, if a similar mechanism is present in humans.

In contrast to these repressive activities, studies have also shown that H3K36 methylation can recruit complexes that participate in establishing a permissive or active chromatin environment and other functions of active transcription (e.g., splicing). As one example, a PWWP-containing subunit of the MOF histone acetyltransferase complex, BRPF1, can bind H3K36 methylation and this interaction

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is important for the expression of *Hox* genes in mice [95]. In addition, and in *Drosophila melanogaster*, H3K36 methylation also participates in dosage compensation. Unlike in human females where one of the two X chromosomes is silenced, the sole X chromosome is upregulated in *Drosophila* males. H3K36 methylation facilitates this process through the binding of another chromodomain-containing protein MSL3 [96–98]. The exact mechanism of how MSL3 binding leads to increased expression is still not fully known, but it is thought to occur in part through increased transcription elongation [99]. Taken together, although a major role of H3K36 methylation during active transcription is to recruit proteins that maintain a closed chromatin environment, the studies above also highlight the ability of H3K36 methylation to regulate increased transcription through recruitment of a histone acetyltransferase complex.

Interestingly, studies on the role of histone PTMs in splicing have shown that SETD2-mediated H3K36me3 is enriched in excluded exons in humans [100,101]. This mechanism occurs through the recognition of H3K36 methylation by the chromodomain-containing protein MRG15. Binding of H3K36 methylation by MRG15 leads to the recruitment and binding of the polypyrimidine tract binding protein (PTB) to splicing silencer sites to exclude the marked exon [100,101]. In contrast, another study in *Caenorhabditis elegans* found that H3K36me3 marks included exons [102]. Thus, like its role in transcription elongation, H3K36 methylation may play a multifaceted or context dependent role in splicing.

Lastly, as with H3K4 methylation, each methylation state of H3K36 may play a distinct biological function. Consistent with this idea and as mentioned above, studies using budding yeast have shown that H3K36me3, but not H3K36me2, is dispensable for the recruitment of the Rpd3S complex — thereby suggesting a different role for H3K36me2 and H3K36me3 [82,83]. Importantly, H3K36me2 is associated with gene bodies regardless of transcription frequency, whereas H3K36me3 is highly correlated with the transcription rate [17,71]. Thus, while H3K36me2 may function to maintain a basal repressive chromatin environment, it is interesting to speculate that H3K36me3 triggered by high transcription levels serves to recruit a distinct set of reader proteins to further promote or maintain active transcription. One such reader for H3K36me3 may be the NuA3 acetyltransferase complex, which contains a PHD finger in the Nto1 member of this complex that has been shown in vitro to bind H3K36me3 [52]. Furthermore and consistent with this observation, studies show that the NuA3 complex depends, at least in part, on H3K36 methylation (in addition to the aforementioned H3K4 methylation) for its chromatin engagement [103]. It is not yet clear, however, what additional role, if any, the NuA3 complex could play in gene bodies during high levels of transcription. Finally, the lowest methylation state of H3K36, H3K36me1, in budding yeast has been reported to function in DNA replication origin function, but the reader mediating this function has not been identified [104]. These findings, taken together, suggest multiple functions for the H3K36 methylation states, although effector proteins that specifically read the higher and lower H3K36me states have not been well defined.

4. Gene body methylation — H3K79 methylation as a protection from silencing

Another modification found in gene bodies is methylation of H3K79 (Fig. 1), however, unlike H3K36 methylation, its role in actively transcribed genes is less clear. All three methylation states of H3K79 are catalyzed by a single histone lysine methyltransferase, which in yeast is Dot1 and in humans DOT1L [105–108]. Despite the lack of a clear role in active transcription, H3K79 methylation is regulated by transcription associated proteins including the PAF complex and the histone H2B ubiquitin ligases Rad6 and Bre1 [109]. Furthermore, a member of the H3K4-methylating COMPASS complex, Cps35/Swd2, promotes H3K79 methylation, and is capable of binding Dot1 [110]. In complex organisms, Dot1 has been found to be associated with transcription elongation machinery and RNAPII, providing a direct link between H3K79me and RNAPII transcription [111,112]. In addition to a role in active transcription, Dot1 and H3K79 methylation were originally identified as important for the establishment and maintenance of silenced regions especially at telomeres and has since been implicated in the DNA damage response, DNA replication and transcription [109,113].

The mechanism by which H3K79 mediates its many functions still remains an open question in the field of lysine methylation. The main reason for this is a lack of understanding of how this site is read. One of the most well studied readers of the modification state of H3K79 is Sir3, which is a member of the SIR histone deacetylase complex [114]. Sir3 binds to a nucleosomal surface including the H4 N-terminal tail and histone core residues including H3K79 via its bromo-adjacent homology (BAH) domain [115,116]. Binding of the BAH domain, however, is refractory to all three methyl states of H3K79 [115,117]. Thus, it has been proposed that the presence of H3K79 methylation in euchromatic and sub-telomeric regions is to prevent transcriptional silencing by impairing the binding and/or function of the SIR complex [108,117].

H3K79 methylation has also been discovered to be an important player in leukemias resulting from translocations of the *MLL* genes. In these types of leukemias, the non-catalytic region of MLL becomes fused to one of several transcription-associated DOT1L-interacting proteins [118–120]. These fusion proteins inappropriately recruit DOT1L to the normally silenced *Hox* genes leading to their activation. Aberrant recruitment of DOT1L with accompanied H3K79 methylation is a primary driver of tumorigenesis. It remains to be determined, however, how H3K79 methylation facilitates transcription at target genes. Future studies to identify the proteins that read this modification are needed to better understand the role of H3K79 methylation in transcription.

5. Lysine methylation in context — Combinatorial readout of histone PTMs fine tune transcription

It is clear that histone lysine methylation can be read and interpreted in numerous ways leading to the question of how such robust functionality is achieved. This review so far has focused on lysine methylation in isolation — yet this is far from the situation found in vivo since histones can be multiply modified with unique combinations of PTMs. Studies using mass spectrometry have identified an astounding number of combinations of histone PTMs occurring on single histones, which may explain the specificity that is observed for some histone readers [121,122]. In this regard, the presence of unique combinations has been proposed to constitute a 'histone code' where unique combinations of histone PTMs can guide distinct cellular functions [123,124]. This hypothesis may help to explain examples of apparent contradictory functions of a single site of lysine methylation.

Histone reader proteins are able to interpret the combinations of histone PTMs or 'histone code' in multiple ways — either through one reader domain, or through the combined action of multiple domains. An example of the former is observed in both budding yeast and humans where asymmetric dimethylation of arginine 2 of histone H3 (H3R2me2a) has been shown to perturb the binding of H3K4 methyltransferase complexes to chromatin [125,126]. H3R2me2a is typically associated with repressed chromatin, which helps to ensure that recognition and propagation of H3K4 methylation by the COMPASS and MLL complexes only occur at transcriptionally active promoters. Another example of this is observed for phosphorylation of threonines 3 and 6 of histone H3 (H3T3ph and H3T6ph), where phosphorylation is antagonistic to several H3K4me3 binding proteins [127–131]. Since H3T3ph and H3T6ph both exist during mitosis, this ensures that transcription-associated H3K4me3 binding does not occur during this stage of the cell cycle.

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Another way in which histone readers recognize a specific chromatin context is through the use of paired domains. A common observation among histone reader proteins is the presence of not just one, but many domains that are capable of binding modified histones. One of the most carefully studied examples of this is the H3K4me3 binding protein BPTF. In addition to the PHD finger that binds H3K4me3, this protein also contains another uncharacterized PHD finger as well as a bromodomain, which typically binds acetylated lysine residues. In the case of BPTF, the bromodomain is adjacent to the H3K4me3-binding PHD finger and is able to bind acetylated lysine 16 of histone H4 (H4K16ac) [36]. Thorough biochemical examination has shown that BPTF recognizes both H3K4me3 and H4K16ac within the same nucleosome, despite the two modifications existing on separate histone tails (Fig. 2E). Thus, multiple modifications within a nucleosome can help shape the specificity of nucleosome binding.

Important to mention is the finding that multiple reader domains are not only found within individual proteins, but also within protein complexes as is the case for the aforementioned TFIID complex. This complex is not only able to interpret histone acetylation and methylation through the TAF1 and TAF3 subunits, respectively, but is also able to read DNA sequence through the TATA box binding protein TBP (Fig. 2F) [22–24,26]. The same is also the case for the H3K4 methyltransferase complex SET1A/B, which is able to bind both H3K4me3 and DNA through the CFP1 subunit [51,132]. We note, however, that as opposed to BPTF, the ability of multiple domains within a complex to simultaneously recognize specific chromatin states has yet to be rigorously demonstrated. Nonetheless, these observations illustrate that considering histone modifications and reader domains in isolation is not totally informative of the function of lysine methylation. As a result, generalities with regard to a given PTM may be difficult to make. The combined readout of histone PTMs and DNA modifications is important for determining the functionality of a protein complex and allows for context dependent function.

6. Future perspectives and conclusions

Histone lysine methylation plays an important role in the structure and function of chromatin, in particular and as highlighted in this review, in active transcription. Starting with H3K4 methylation at promoters and enhancers and leading to H3K36 and H3K79 methylation in gene bodies, it is quite surprising given the wide array of known histone PTMs just how these three PTMs can play such diverse roles. The presence of lysine methylation at actively transcribed genes does not tell the entire story, however. It is instead the wide array of proteins that are capable of recognizing lysine methylation that fulfills the function of these PTMs. Lysine methylation can dictate a number of functions that are all related to the further modification of the chromatin structure to either promote or prevent transcription. One of the main questions that still exist regarding histone lysine methylation (as well as other histone PTMs) is to what extent it actually plays in regulating DNA-templated processes. Early studies on transcription in vitro have clearly demonstrated that transcription can occur in the absence of chromatin and histone PTMs. Moreover, loss of the histone lysine methyltransferases in budding yeast does not result in drastic changes in global gene expression [133]. While the latter observation could be the result of the redundancy among histone PTMs, it is more likely due to the idea that histone PTMs play more of a role in fine-tuning transcription and other DNA-templated functions. Thus, histone PTMs like lysine methylation may be more important for dictating the spatial and temporal regulation of transcription to ensure that a given gene is expressed at the right place and time, and that transcription continues only as long as it is needed. That being said, lysine methylation becomes critical at times when the precise timing of gene expression is needed (e.g., cellular stress or development). This idea is supported by studies including a recent work investigating the role of histone PTMs in global transcription during cellular stress [134]. This study found that loss of individual histone PTMs has a greater effect on transcriptional activation or repression in response to stress as opposed to under normal conditions. Moreover it is clear that loss of histone lysine methyltransferases during early animal development can lead to early lethality [135].

To better understand how lysine methylation precisely impinges on transcription, future studies will need to focus on identifying the complete profile of reader proteins for each site of methylation. While much work has been done to focus on both the methylation of H3K4 and H3K36 (as covered in this review) and the repressive modifications occurring at H3K9 and H3K27, much less is known about the readers of other methylation sites. As discussed earlier, one site in particular with relevance to transcription is H3K79. Moreover, other sites of low abundance lysine methylation have been observed with yet to be identified readers.

In addition to identifying the reader proteins of other sites of methylation, future studies will also need to focus further on the types of domains that can read histone methylation. Currently a set of canonical domains have been studied that can bind methylated lysine residues (see Table 1), yet this list continues to grow. Aside from the PHD finger, Tudor, PWWP and chromodomains, other domains such as the BAH and CW domains have been identified to recognize methylated lysine [136,137]. It is likely that yet-to-be characterized domains will be found to engage methyllysine on histones. Thus, a complete profile of the domains that bind methylated lysine will be necessary to fully understand and appreciate the role of histone methylation.

Lastly, methylation has been observed on lysine residues in other nuclear proteins aside from histones [138–140]. This non-histone methylation can be catalyzed by histone methyltransferases adding yet another level of complexity to the study of PTMs in the nucleus. It will be interesting to identify the readers of this new set of PTMs, which will likely provide insight for a broader understanding of the regulation of DNA-templated processes.

In conclusion, histone lysine methylation plays diverse functions in DNA-templated processes. These functions are dependent on how the PTMs are read and interpreted by the cellular machinery. The study of the complex mechanism of regulating chromatin via PTMs has evolved into an exciting and fast paced field of biology, which will likely continue to further expand our basic understanding of the genome.

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