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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]

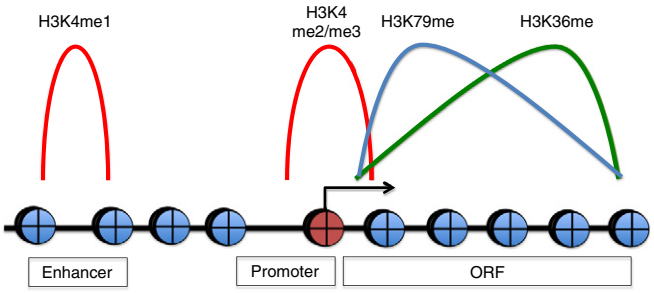

Fig. 1. Distribution of active methylation across genes. Histone lysine methylation exists in distinct patterns in and around actively transcribed genes. Shown is a representative model of a gene region with corresponding enrichment of indicated methylation state. Methylation enrichment reflects patterns 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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