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HISTONE MODIFICATIONS AS KEY REGULATORS OF TRANSCRIPTION

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1. ABSTRACT

Covalent modifications of the amino-termini of the core histones in nucleosomes have been shown to be one of the key regulatory mechanisms in transcription regulation. Recently, new roles for histone modifications have been uncovered for the efficient functioning of RNA Pol II. Besides acetylation, which is the most characterized to date these modifications comprise phosphorylation, methylation, and ubiquitination. This review gives comprehensive view of all the major histone modifications and their effect on transcriptional regulation, in *Saccharomyces cerevisiae*.

2. INTRODUCTION

The organization of the higher order chromatin structure has been linked to the post-translational modifications of histones tails, including acetylation, phosphorylation and methylation and ubiquitination (1). Thus, chromatin could be regarded as regulatory principle that allows the discrimination of transcriptionally active (euchromatin) from transcriptionally inactive (heterochromatin) regions in a way to facilitate the execution of gene expression programmes (2) and to direct the establishment of specialized structures such as centromere and telomeres (3).

The fundamental structural unit of chromatin is nucleosome which is comprised of a core histone octamer (H2A, H2B, H3 and H4) and the associated DNA that wraps around them. Histone H1 helps to further packaging of nucleosomes into 30 nm fibers with six nucleosomes per turn in a spiral or solenoid arrangement (4, 5). The unfolding of 30 nm fibers generates a template for transcription. In this review we are focusing on N-terminal histone tail modification. Unlike the dynamic "On and off" nature of histone acetylation, early studies found that mammalian histones H3 and H4 were highly methylated with little turnover of methyl groups (6, 7). The apparent stability of methylation in bulk histone preparations led to the belief that this was a generic and steric modification. In contrast, some other findings revealed that histone methylation, like histone acetylation, is a dynamic process involved in a number of diverse biological processes including transcriptional regulation, chromatin condensation, mitosis and heterochromatin assembly (8-12).

Since recent studies have revealed histone modification as an important regulator of chromatin function, and till date these studies documented histone methylation as plying both positive and negative roles in the process of gene processing. Therefore, we are reviewing all the information that would definitely help to understand the insight of gene silencing and transcription regulation.

3. CONCEPT OF EPIGENETICS

It is now recognized that heritable but reversible, changes in gene expression can occur without alterations in DNA sequence. Studies on radiation induced chromosomal translocation (12) provided some of the earliest findings that epigenetic " On and Off" transcriptional state are largely dependent on the position of a gene within an accessible (euchromatic) or an inaccessible (Heterochromatic) chromatin environment. This phenomenon is called position effect variegation (PEV). It allows the development of genetic screens in *Drosophila* (13)and *S. pombe* (14, 15) that have identified ~30 to 40 loci involved in modifying PEV. Mating-type switching in budding and fission yeast represents another model for a variegating mechanism where the location of gene within a distinct chromatin environment, the mat region, dictates the establishment of an active or a silent transcriptional state (16, 17). Especially for *S. pombe*, which appears to contain a higher order chromatin structure more closely resembling that of multicellular eukaryotes, inheritance of silenced chromatin domains has been shown to be remarkably stable during both mitosis and meiosis (17).

4. ACETYLATION

Allfery and colleagues, more than 30 years ago, showed that increased histone acetylation caused to increase

Table1. Histone modifications

Histone	Residue	Modification	Associated protein(s)/modules	Function
H2B	K123	Ubiquitination	Bre1, Rad6, Set1	Transcription
H3		Unmodified	Sir3/Sir4/Tup1	Silencing
H3	K14	Acetylated	Bromodomain	Transcription
H3	K9	Acetylated	???	Histone deposition?
H3	S10, S28	Phosphorylation	SMC/Condensins	Mitosis/meiosis
H3	S10, K14	Phos/Acetyl	???	Transcription
H3	K4, K36, K79	Methylation	Set1, Set2, Dot1	Transcription
H3	???	Higher order combinations	???	Differentiation?
H4	K8, K16	Acetylated	?	Transcription
H4	K5, K12	Acetylated	RCAF?	Histone deposition
CenP-A	S7? S17-S27	Phosphorylated	?	Mitosis

transcription (18). Several groups have elucidated the mechanism by which histone acetylation and deacetylation regulate gene activity (Table 1). Many of the enzyme that catalyze histone acetylation and deacetylation have been identified as transcriptional co-regulators (19). The fact that HATs are coactivators rather than DNA-binding moieties underscores the need for flexibility, regulation and alternative strategies in regulating chromatin and the basal transcriptional machinery.

Most of the HATs are components of large multisubunit complexes, which are recruited to the promoters by interaction with DNA-bound activators (20). SAGA/ human PCAF/Gcn5 and NuA4/human Tip60 complexes are the two well-studied examples, which have role in transcription (21, 22). Earlier studies have shown that there are several interaction surfaces within the complexes for association with activators. Recently it was discovered that Tra1/TRRAP protein is most likely the predominant direct target of activators (23, 24). Later, HATs associated proteins were also identified as co-activator of TATA binding protein (TBP) or other general transcription factors on the basal promoter (25). Moreover, SAGA has also been shown to have non-chromatin-dependent co-activator activity that means if promoters that do not require Gcn5's acetylation activity, other components of the SAGA complex are required for complete transcription via TBP recruitment (26, 27). Although the identity and mechanism of action has dominated the field of chromatin modification in the past five years, the next stage of discovery will be the biological role of these enzymes in higher eukaryotes, including connection to disease.

5. PHOSPHORYLATION

Modification of Histones by phosphorylation was first seen in late sixties (28) and kinase responsible for this modification was identified as a AMP dependent kinase (29). Subsequently, many researchers have identified many H3-kinases able to phosphorylate H3 serine-10 both *in vivo* and *in vitro* (Figure 1) (30-32). These kinases can be functionally divided into kinases that function in signal transduction and mitosis, which suggests that H3ser-10 phosphorylation might have multiple functions (33). Earlier studies have shown that histone phosphorylation has a role in transcriptional induction of immediate early genes in mammalian cells, such as the *c-Fos* gene (34). The Rsk/Msk family of protein kinases have been shown to regulate the phosphorylation directly (35, 36). It has been shown in *Drosophila* that there is a dramatic increase in H3 ser-10 phosphorylation at heat shock induced promoters (37). Recently a PP2A phosphatase has been shown to regulate the phosphorylation of the H3 Ser-10, thereby affecting the transcription (38).

Histone phosphorylation in yeast involving H3 Ser-10 has also emerged as an important modification, both in transcription activation and in chromosome condensation during mitosis (Table1) (33). A transcriptionally-linked histone kinase has been identified in *S. cerevisiae* as the previously well known Snf1, a kinase involved in glucose metabolism (39). The involvement of the histone kinases as transcriptionally associated factors suggest the possibility of recruitment of these kinases to specific promoters as coactivators.

6. UBIQUITINATION

Ubiquitination has been found associated with many cellular processes including protein degradation, DNA repair, Cell cycle control, stress response and now transcription regulation (40-42). Histone ubiquitylation has now been included in the group of important modifications of histone. It has been shown recently that H2B lysine 123 gets mono ubiquitinated by Rad6 (Fig.1), a E2 ubiquitin ligase (43). This modification has been shown to be functionally important for mitotic and meiotic growth. However its importance in transcription was not known until now. Recent reports suggest that H2B K123 ubiquitination is important prerequisite for recruitment of PAF complex thereby regulating the elongation of RNA polymerase II (44-46). It also showed that this modification of H2B K123 is critical for H3 K4 methylation mediated by Set1 (44-47). A very recent report has shown that histone H2B ubiquitination and deubiquitylation is involved in transcription activation and that Ubp8 of SAGA complex is involved in deubiquitylation of UbH2B (48). The finding that both H2B ubiquitination and deubiquitylation are involved in transcriptional activation is very surprising, because removal of histone modifications typically opposes the effect of their addition such as acetylation/deacetylation. It

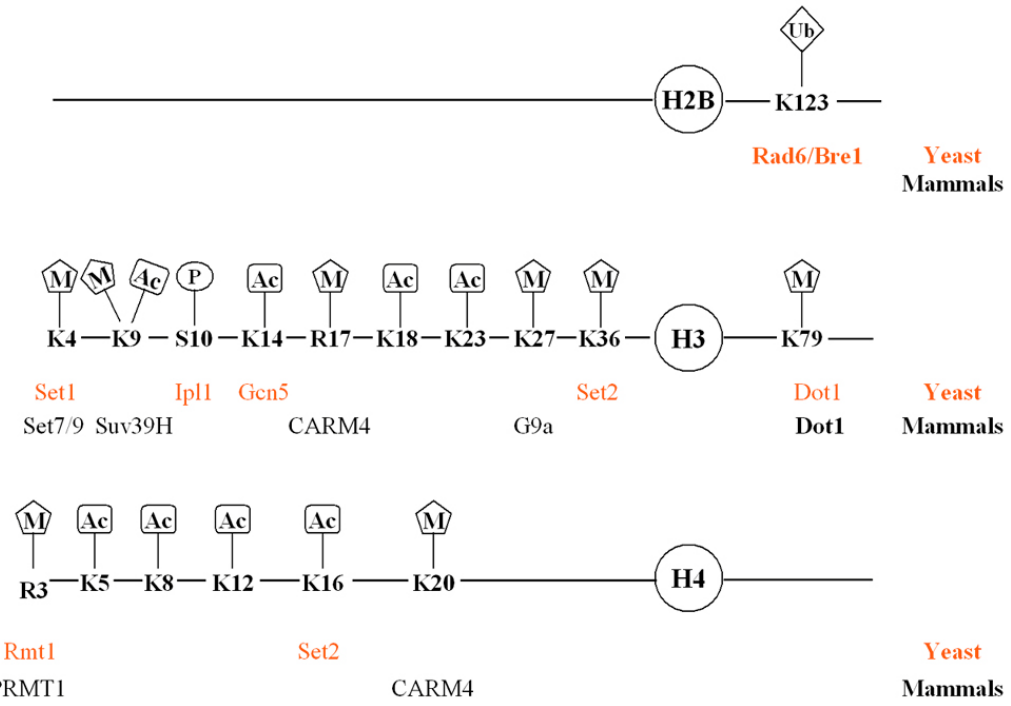

Figure 1. Overview of histone modifications. Methylation (M), acetylatio (A), phosphorylation (P), and ubiquitination (U). Mammalian proteins that catalyze the respective modifications are indicated with black colour, whereas, proteins from *S. cerevisiae* are shown by red colour. Modified from of Khan and Hampsey (69).

has been proposed that deubiquitylation may serve to 'reset' the promoter region to a lowered level of ubiquitinated H2B, during induction of highly transcribed genes (48).

Earlier, added to its other histone modifying enzymatic activities (like kinase, and HAT activity), ubiquitination activity of TafII250 of TBP associated TFIID complex on Histone H1 was shown, in Drosophila (49), which may be involved in transcription.

7. HISTONE METHYLATION

There are two types of histone methylation, targeting either arginine or lysine residues. Methylation of these two residues has been shown to regulate transcription. These are CARM1/PRMT1 and SET family and they predominately target either H3 or H4 (Fig.1). The biological role of H3 Lys4 methylation is to regulate RNA polymerase II transcriptional silencing with rDNA, a specialized chromatin structure known to mediate this biological effect (50-52). Mutation in H3 at Lys4 or *set1*△ strain both show similar defect, indicating that set1-mediated H3Lys4 methylation is important for cell growth, transcription regulation, DNA repair, meiosis (53-55). In contrast COMPASS seems to be required for silencing of gene expression at telomeres (53, 54, 56). Moreover, Allis and colleagues have recently demonstrated that methyl-Lys4 histone H3 is present at rDNA locus, and that this modification is required for silencing of RNA polymerase II transcription of a gene located within rDNA locus (57, 58). However, the exact mechanism of set1 mediated H3 Lys4 methylation in regulating cell growth and the specialized chromatin structure of rDNA is not known. Binding of a yet unknown silencing factor(s) to H3 methylated at Lys4 may occur in much the same way as the chromatin of HP1 or Swi6 recognizes and binds to Lys9-methylated H3 to establish heterochromatin domain (11, 59-61).

Yeast *SET*1 has been mainly implicated in transcriptional repression (53, 54) whereas methylation at lysine 4 has been implicated in transcriptional activation (62). ySet1 has methylase activity directed against lysine 4, is responsible for stimulating transcription . Santo-Rosa et al carried out a genome-wide microarray analysis to identify genes whose activity is reduced in the absence of ySET1 (*set1*△) (63). Among the 20 genes whose transcription is reduced between 1.6-2.1 fold in *set1*△ strain relative to wild type, PPH3 gene was the most affected one (63).

The plausible mechanism of transcription activation by lysine 4 methylation (64) is that methylation of lysine 4 regulates the binding of other proteins to histone H3. Mono-, di- and tri-methylation of histone lysine residues appear to be catalyzed by specific enzymes with different biological outcomes (64). For example human Set9 catalyzes di- and tri- methylation of the same residue. H3-K4 dimethylation appears to be global, whereas H3-K4 tri-methylation is associated with the early stages of transcription (63, 65). We propose a model on the function

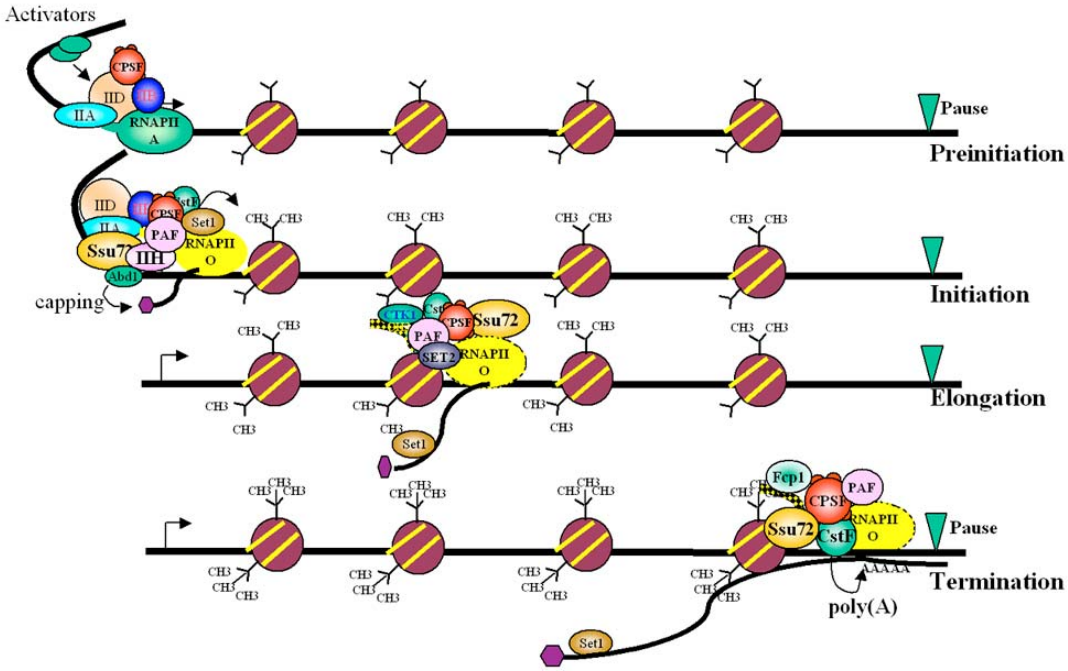

Figure 2. A model proposed to explain the role of Set1 and Set2 in Pol II transcribed gene regulation. Name of the proteins are indicated in the oval or circular shapes. Different colour for different proteins are used. Purple balls are histone octamer wrapped around with DNA (yellow strips). Small purple hexagon is 5' cap of nascent RNA. This model explain the role of different transcription factors and regulation of transcription by methylation of histone H3 at specific sites (Set1 at Lysine 4 and Set2 at Lysine 36). Initiation complex is formed to initiate the transcription followed by elongation and termination of newly synthesized RNA.

of H3-K4 tri-methylation (Figure 2). It is likely that Set1-mediated tri-methylation is involved in the regulation of initiation and promoter clearance. Moreover, Set1 itself has been shown to have an RNA recognition motif (66). Hampsey and Reinberg have recently hypothesized that Set1 binds to nascent RNA as it emerges from RNAP II, perhaps freeing the PAF complex to modulate downstream events (67). In this manner, the Set1 complex might remain with the nascent mRNA and participate in formation of the mature 3' end. This idea is supported by other observations in machinery associated with RNAP II in the early stages of transcription (68). Second, histone methyltransferase complexes that establish silencing are tethered to chromatin, suggest a possible role for H3-K4 methylation in orchestrating the recruitment of 3'-end processing factors.

Another protein of SET family was reported, Set2, a nucleosomal H3 methyltransferase that is highly selective for H3-K36 (62). It physically associates with RNAP II and that this interaction is regulated by PAF complex and Ctk1. It was speculated that H3-K36 methylation participates in both modes of regulation. It is possible that H3-K36 provides, directly or indirectly, a docking site for the association of Ctk1, maintaining hyper-phosphorylation of the RNAP II CTD. In this way, the H3-K36 and CTD modifications might allow recruitment of enzymes required for the splicing and polyadenylation reactions.

8. PERSPECTIVE

Extensive studies have revealed that histone modification plays important roles in diverse processes ranging from transcription regulation, chromatin organization, to genomic imprinting and X chromosome inactivation (70,71). Although the progress in the studies of histone modification has been impressive, there is still much more need to be understood regarding the biological function as well as mechanisms of histone modification-based regulation.

The initial notion that histone acetylation is a regulatory mechanism for gene expression has now expanded in many ways. In the present scenario histone phosphorylation, methylation and ubiquitination have each been correlated with gene regulation. Histone acetylases can be basic components of, or closely associated with, the Pol II machinery. Thus, recruitment of the Pol II machinery to promoters is concomitant with recruitment of histone acetylases, thereby providing a simple mechanism to account for the general correlation between histone acetylation and transcriptional activity. Future revelations will identify new modifications of specific residues in the tails of histones H3 and H4, and will likely indicate modifications in both the amino and extended carboxy-terminal tails of H2A and H2B. Interconnection and interdependence of modifications in the H3 and H4 tails, suggesting specific modification state, which is characteristic of transcriptional regulation.

Very rapid progress has been made in the field of histone modification but much must still be accomplished. This is clearly an important event in the transcriptional response. What needs to be established is its precise mechanism of action, the biological functions it may be involved in and its relevance in cancer and other diseases.

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