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Review

The role of histone H2A and H2B post-translational modifications in transcription: A genomic perspective

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In eukaryotic cells, the genome is packaged with histones H2A, H2B, H3, and H4 to form nucleosomes. Each of the histone proteins is extensively post-translationally modified, particularly in the flexible N-terminal histone tail domains. Curiously, while post-translational modifications in histone H3 and H4 have been extensively studied, relatively little is known about post-translational modifications in the N-terminal domains of histone H2A and H2B. In this review, we will summarize current knowledge of post-translational modifications in the N-terminal domains of histone H2A and H2B, and the histone variant H2AZ. We will examine the distribution of these modifications in genomic chromatin, and the function of these modifications in transcription.

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1. Introduction

The fundamental building block of chromatin is the nucleosome core particle, which is comprised of 147 bp of DNA spooled around a hetero-octamer of histones H2A, H2B, H3, and H4. In the nucleosome structure, histones H3 and H4 form a hetero-tetramer that is flanked by two histone H2A and H2B hetero-dimers [1]. The H3–H4 tetramer forms the core of the nucleosome structure, interacting with the middle and both ends of the nucleosomal DNA. The histone H3 and H4 N-terminal domains, which exit the nucleosome near the DNA entry and exit points, are highly modified at multiple residues. For example, in the human histone H3 N-terminal domain there are four methylated lysine residues (K4, K9, K27, and K36), three methylated arginine residues (R2, R17, and R26), two phosphorylated serine residues (S10 and S28), two phosphorylated threonine residue (T3 and T11), and four acetylated lysine residues (K9, K14, K18, and K23) [2–4]. Histone H3 and H4 post-translational modifications have been the subject of intense scrutiny, due to their perceived importance in controlling gene expression. Many studies have linked histone H3 and H4 modifications to transcriptional regulation, heritable epigenetic silencing, and the development of human disease, including cancer (reviewed in [5,6]).

In contrast, the histone H2A and H2B dimers are more weakly associated with nucleosomal DNA [7–10] and more frequently displaced from nucleosomes [11–17], suggesting that post-translational modifications present on these histones are less likely to be stably propagated in chromatin. H2A–H2B dimers bind to interior segments of the nucleosomal DNA that are relatively distant from the crucial nucleosome entry and exit points [1]. Perhaps for these reasons, post-translational modifications in the N-terminal domains of histone H2A and H2B have been relatively neglected in the scientific literature. Recent studies of yeast histone H2A and H2B mutants [18,19], however, should stimulate a re-evaluation of the importance of these histones, and their N-terminal domains, in transcriptional regulation.

In this review, we will first summarize the results of genome-wide expression profiling studies that highlight the importance of the H2A and H2B N-terminal domains in transcriptional regulation. Second, we will describe the post-translational modifications that have been identified in these N-terminal domains, and discuss their functional significance. Third, we will discuss the results of chromatin immunoprecipitation microarray (ChIP-chip) experiments, which have mapped the genome-wide pattern of histone H2A and H2B post-translational modifications in chromatin, and address the question of whether histone H2A and H2B modification patterns provide regulatory information that is distinct and independent from histone H3 and H4 modifications. Fourth, we will report on studies examining the role of histone H2A and H2B N-terminal modifications in regulating genome transcription. Finally, we will examine the

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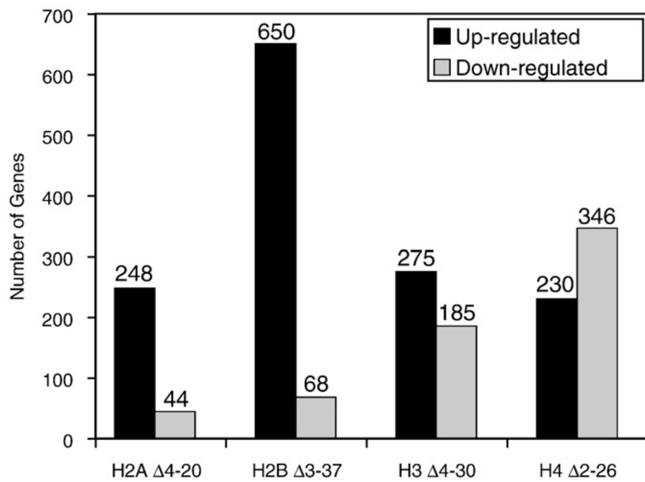

Fig. 1. Comparison of the number of differentially expressed genes in each histone N-terminal deletion mutant. Published microarray data for H2A Δ4–20 [19], H2B Δ3–37 [18], H3 Δ4–30 [24], and H4 Δ2–26 [23] are displayed. Data for H4 Δ2–26 [23] were processed to remove redundant gene entries.

distribution and function of post-translational modifications in the histone H2A variant H2AZ.

2. Importance of histone H2A and H2B N-terminal domains in transcriptional regulation

It is difficult, particularly in higher eukaryotes, to discern the contributions that each histone N-terminal domain makes to transcriptional regulation. This difficulty is due, in part, to the broad substrate specificity of many histone modifying enzymes. For example, the KAT2 (Gcn5/PCAF) histone acetyltransferase (HAT) acetylates multiple residues located in the histone H2B and H3 N-terminal tails [20–22]. Hence, it is unclear whether KAT2 regulates transcription through acetylating histone H3 or histone H2B (or both). Similarly, many histone deacetylases (HDAC) have broad substrate specificity: class I histone deacetylases such as Rpd3 can deacetylate lysine residues on all four core histone proteins [20,21]. Hence, the gene expression changes caused by treatment of cells with histone deacetylase inhibitors could, in principle, be mediated by acetylation changes at any of the four core histone proteins.

This ambiguity can only be resolved by examining site-specific mutants in the histone proteins themselves. The yeast *S. cerevisiae* provides an excellent model system to study histone mutants. Recent studies in yeast have examined the effects of N-terminal deletion mutants in each core histone protein on global gene expression [18,19,23,24], which for the first time enables one to discern the relative contributions of each histone N-terminal domain to transcriptional regulation.

A simple method for measuring the relative importance of each histone N-terminal domain in gene regulation is to compare the number of genes differentially expressed in the histone mutant strains. This comparison is shown in Fig. 1. Remarkably, these data indicate that the histone H2A and H2B N-terminal mutants affect the expression of similar numbers of genes as the histone H3 or H4 N-terminal mutants. This is particularly apparent for the histone H2B N-terminal mutant, which affects the expression of a relatively large number of yeast genes. It is important to note that the histone H3 [24] and histone H4 [23] mutant data sets were analyzed using different criteria to identify differentially expressed genes. However, if we apply these criteria to the histone H2A and H2B microarray data sets, roughly similar results are obtained (data not shown). We also note that the histone H2A and H2B N-terminal domains function primarily to repress transcription, as reflected by the strong bias towards up-regulated genes in these N-terminal deletion strains (Fig. 1). This is in contrast to the results for the histone H3 and H4 N-terminal domains, which appear to have a more balanced role in activating and repressing gene transcription.

Hence, this simple comparison suggests that the histone H2A and H2B N-terminal domains have a much more significant role in regulating gene transcription than has been previously recognized. This is particularly true for the histone H2B N-terminal domain, which plays a prominent role in yeast transcription relative to histone H3 and H4.

3. Post-translational modifications in histone H2A and H2B

Unlike histones H3 and H4, the N-terminal sequences of histone H2A and H2B show considerable sequence divergence between yeast and mammals. Despite the low degree of sequence similarity, many of the post-translational modification sites in the H2A and H2B N-terminal domains appear to be roughly equivalent between the two species. Fig. 2 summarizes the histone H2A and H2B post-translational modification sites identified in yeast and human histones. As modifications in the C-terminal domains of these histones have been discussed in recent reviews [25–28], we will focus our discussion on modifications in the N-terminal domains of histone H2A and H2B.

In *S. cerevisiae*, two lysine residues in the histone H2A N-terminal domain are acetylated: H2A K4 and K7 [20,29,30]. H2A K4 is acetylated by ScKAT5 (Esa1) [31], while H2A K7 is acetylated by ScKAT1 (HAT1) and ScKAT5 [20,29,31]. Both residues are deacetylated by Rpd3 [29], a class I HDAC.

The equivalent lysine residues in human histone H2A (H2A K5 and K9) are also acetylated (Fig. 2), though histone H2A K9 acetylation has yet to be extensively characterized. Human H2A K5 is acetylated by hKAT5 (TIP60) and hKAT3 (CBP/p300). Human histone H2A is phosphorylated at H2A S1 by the MSK1 kinase [32], and methylated at H2A R3 by PRMT5 [33].

Histone H2B is modified at multiple residues in its N-terminal domain (Fig. 2). In *S. cerevisiae* histone H2B is acetylated at six lysine residues: H2B K6, K11, K16, K17, K21, and K22 [20,29,30,34]. Histone H2B K6, K11, K16, K17, and K22 are acetylated by ScKAT2 (Gcn5) [20,30,35], and H2B K11 and K16 are deacetylated by Rpd3 [20] and the class II HDAC Hda1 [36,37]. H2B K11 is also deacetylated by the Hos3 HDAC under specific environmental conditions (see below). In

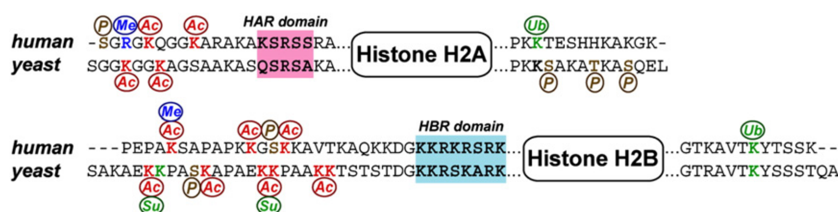

Fig. 2. Summary of post-translational modifications in histone H2A and H2B.

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