CHAPTER 16

HISTONE ACETYLATION AND METHYLATION
Combinatorial players for transcriptional regulation

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Abstract: Post-synthetic modification of histone proteins in chromatin architecture plays a central role in the epigenetic regulation of transcription. Histone acetylation and methylation are the two major modifications that function as a specific transcription regulator in response to various cellular signals. Albeit the mechanism of action of these modifications in transcription is not well understood, recent discovery of histone acetyltransferase (HAT) and methyltransferase (HMT) activities within transcriptional regulators has an important implication for histone modification to be a key player for the precise regulation of transcription processes. Here, we discuss recent advances made on histone acetylation and methylation as a fundamental process to modulate gene transcription, with a particular emphasis on their combinatorial effects in transcriptional control.

1. INTRODUCTION

In eukaryotic cells, the DNA is compacted into the nucleus as a complex structure known as chromatin. The fundamental repeating unit of chromatin is the nucleosome, which consists of 146 bp of DNA wrapped around a core histone octamer containing pairs of each of the histone proteins, H2A, H2B, H3 and H4 (van Holde, 1988; Luger et al., 1997; Kornberg and Lorch, 1999). Structured central domains of core histones mediate histone-histone interactions to stabilize the histone octamer within the nucleosome core particle. Each core histone also contains unstructured N-terminal tail domains ranging from 15 (H2A) to 35 (H3) amino acids, which are extended out of the nucleosome particle (Luger and Richmond, 1998). Although histone tails at the surface of the nucleosome do not contribute to structure and stability of nucleosomes, they are required for the internucleosomal interaction to facilitate the higher-order folding of chromatin fibers (Hansen, 2002).

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A high proportion of the positively charged basic amino acids lysine and arginine within these flexible tails are frequent targets for extensive posttranslational modifications (Berger, 2002). Such modifications include the acetylation of lysine residues, the methylation of lysine and arginine residues, the ubiquitination of lysine residues, the phosphorylation of serine and threonine residues, the sumoylation of lysine residues, and the poly ADP-ribosylation of glutamic acid residues.

Acetylation and methylation of specific lysine or arginine residues in histones H3 and H4 are reversible post-translational processes directly linked to either active or repressive states of gene transcription (Peterson and Laniel, 2004). Although it remains unclear to what extent, it also has been well documented that these modifications mutually affect each other in many cases to regulate specific transcription-based processes (Zhang and Reinberg, 2001; Berger, 2002; Fischle et al., 2003). In the wake of several pioneering techniques, it has been feasible to characterize the contribution of particular histone modifications in transcriptional regulatory networks and to profile the genome-wide status of a specific modification in a massively parallel way. The results of such analyses will be useful in confirming functional consequences of epigenetic signals within histone tails and will ultimately be valuable for diagnostic, therapeutic and drug development purposes. In this article, I will review the individual and combinatorial characters of histone acetylation and methylation in transcription and discuss the implications of epigenetic approaches that target HMT and HAT for the treatment of major pathologies.

2. HISTONE ACETYLATION AND TRANSCRIPTION

Histone acetylation is one of the major histone modifications that takes place at the ε-amino groups on specific lysine residues at the N-terminus of histone proteins (Fig. 1) (Sterner and Berger, 2000; Roth et al., 2001). This modification occurs on all four core histones and reduces the net positive charge on the histone proteins. Earliest studies on this modification suggested that the addition of an acetyl group to a histone N-terminal tail plays some special role in chromatin reorganization for efficient transcription (Allfrey et al., 1964). In support of this idea, histones within active chromatin regions appear to be acetylated to a higher degree than those in inactive chromatin regions (Grunstein, 1997; Kuo and Allis, 1998). Further evidence in favor of a role for histone acetylation in transcription has been obtained by identification of histone acetyltransferases capable of adding acetyl groups to histone tails (Sterner and Berger, 2000; Roth et al., 2001). Observation that many known transcription cofactors possess an intrinsic HAT activity supported the causal relationship between histone acetylation and gene transcription (Table 1). Histone acetylation is a highly dynamic event as a consequence of the presence of histone deacetylases (HDACs) which can induce the removal of acetyl groups from histones (Yang and Seto, 2003); treatment of cells with HDAC inhibitor sodium butyrate has been shown to increase DNase I sensitivity of chromatin and to activate previously repressed genes (Roth et al., 2001). Hence, albeit imperfectly proven, there is a great deal of information to support a positive role for histone acetylation in transcription.