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Review

# Lateral Thinking: How Histone Modifications Regulate Gene Expression

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**The DNA of each cell is wrapped around histone octamers, forming so-called 'nucleosomal core particles'. These histone proteins have tails that project from the nucleosome and many residues in these tails can be post-translationally modified, influencing all DNA-based processes, including chromatin compaction, nucleosome dynamics, and transcription. In contrast to those present in histone tails, modifications in the core regions of the histones had remained largely uncharacterised until recently, when some of these modifications began to be analysed in detail. Overall, recent work has shown that histone core modifications can not only directly regulate transcription, but also influence processes such as DNA repair, replication, stemness, and changes in cell state. In this review, we focus on the most recent developments in our understanding of histone modifications, particularly those on the lateral surface of the nucleosome. This region is in direct contact with the DNA and is formed by the histone cores. We suggest that these lateral surface modifications represent a key insight into chromatin regulation in the cell. Therefore, lateral surface modifications form a key area of interest and a focal point of ongoing study in epigenetics.**

## Trends

The globular domains of histones represent the emerging front of histone modification research.

Modifications in the globular domains of histones can directly affect transcription and nucleosome stability.

Many globular domain modifications also have roles in the DNA damage response, stemness, leukaemia and cell differentiation.

Novel modifications, such as arginine methylation, are also present in this region and can directly affect the compaction of the DNA coating the nucleosome.

## The Nucleosome: How to Package a Genome

Each diploid human cell contains approximately 2 m of DNA [1], which must be accessed when needed, for instance for transcription or replication. This requires that the transcriptional or replication machinery get to the required genomic regions at the correct time, despite the generally highly compacted DNA within the nucleus of the cell. Early studies showed that DNA, despite its natural tendency to become disordered [1], is organised into tightly regulated structures [2,3]. This organisation begins with the wrapping of the DNA around an octameric protein complex, forming a so-called 'nucleosomal core particle' [4]. Each of these contains two of each core histone (H2A, H2B, H3, and H4 [5–7]) with 145–147 base pairs (bp) of DNA wound around it. A histone known as linker histone H1 is bound to the outside of the nucleosome core particle, forming a full nucleosome or chromatosome, and stabilising higher-order chromatin structures [4,8]. Nucleosomes are found every 200 ± 40 bp [9] and they form a characteristic 'beads on a string' structure with their coating DNA [10].

In general, nucleosomes impede transcription of the DNA [11,12]. They may do this by physical obstruction, as well as by bending the DNA, thus reducing its availability to transcription factors [5]. However, histones can also carry many post-translational modifications and these can influence chromatin compaction and accessibility in many different ways. These modifications include acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, ADP ribosylation, and deamination [13]. More recently, other modifications, such as propionylation and butyrylation, have been described [14]. So far, the best-studied modifications are those that

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Table 1. Histone Tail Modifications

| Histone | Modification | Role | Refs |
|---|---|---|---|
| H2A | H2AS1P | Mitosis; chromatin assembly | [98] |
| | H2AK4/5ac | Transcriptional activation | [99] |
| | H2AK7ac | Transcriptional activation | [100] |
| | H2AK119P | Spermatogenesis | [101] |
| | H2AK119uq | Transcriptional repression | [102] |
| H2B | H2BS14P | Apoptosis | [103] |
| | H2BS33P | Transcriptional activation | [104] |
| | H2BK5ac | Transcriptional activation | [105] |
| | H2BK11/12ac | Transcriptional activation | [100] |
| | H2BK15/16ac | Transcriptional activation | [100] |
| | H2BK20ac | Transcriptional activation | [105] |
| | H2BK120uq | Spermatogenesis/meiosis | [101] |
| | H2BK123uq | Transcriptional activation | [106] |
| H3 | H3K4me2 | Permissive euchromatin | [107] |
| | H3K4me3 | Transcriptional elongation; active euchromatin | [26,107–109] |
| | H3K9me3 | Transcriptional repression; imprinting; DNA methylation | [26,110] |
| | H3R17me | Transcriptional activation | [111,112] |
| | H3K27me3 | Transcriptional silencing; X-inactivation; bivalent genes/gene poising | [26] |
| | H3K36me3 | Transcriptional elongation | [26] |
| | H3K4ac | Transcriptional activation | [109] |
| | H3K9ac | Histone deposition; transcriptional activation | [100] |
| | H3K14ac | Transcriptional activation; DNA repair | [26] |
| | H1K18ac | Transcriptional activation; DNA repair; DNA replication | [26] |
| | H3K23ac | Transcriptional activation; DNA repair | [26] |
| | H3K27ac | Transcriptional activation | |
| | H3T3P | Mitosis | |
| | H3S10P | Mitosis; meiosis; transcriptional activation | [110] |
| | H3T11/S28P | Mitosis | |
| H4 | H4R3me | Transcriptional activation | [87] |
| | H4K20me1 | Transcriptional silencing | [113] |
| | H4K20me3 | Heterochromatin | [114] |
| | H4K5ac | Histone deposition; transcriptional activation; DNA repair | [100,115] |
| | H4K8ac | Transcriptional activation; DNA repair; transcriptional elongation | [100,115] |
| | H4K12ac | Histone deposition; telomeric silencing; transcriptional activation; DNA repair | [100,115] |
| | H4K16ac | Transcriptional activation; DNA repair | [16,100,115] |
| | H4S1P | Mitosis | [98] |

occur on the N-terminal 'tail' regions of the histones, which project from the nucleosome and are accessible on its surface [5] (Table 1 and Figure 1). Some of the modifications in these tails can directly affect the interactions between nucleosomes. For example, the addition of acetyl moieties to lysine 16 of histone H4 (H4K16ac) has been shown to reduce chromatin compaction [15] and increase transcription both *in vitro* and *in vivo* [16]. Histone tail modifications can also do