Mini Review

A mini review on post-translational histone modifications

Abstract

Eukaryotic DNA is packaged into chromatin, folded and compacted. Formation of higher order chromatin not only results in condensing DNA, but also affects its functionality since certain regions of DNA are no longer accessible whereas some other regions will be more accessible for e.g. effector proteins to bind. Histones, the building blocks of mammalian chromatin, are small basic proteins that can be covalently modified by methylation, acetylation, phosphorylation, ubiquitylation etc. at their flexible N- or C-terminal tails as well as globular domains. Posttranslational modifications (PTMs) of histones are key players in the regulation of chromatin function. The modulation of chromatin dynamics by histone PTMs and their mechanisms of action have attracted great attention. Previous studies implicated histone PTMs in a variety of cellular processes such as transcription, DNA damage, apoptosis, and cell cycle regulation. Perturbations in the regulation of chromatin modifiers cause defects in these cellular processes and hence can result in diseases, suggesting epigenetic regulators as drug novel therapy targets.

Keywords: chromatin, epigenetics, histone, post-translational modification, ptm

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Abbreviations: PTM, posttranslational modification; RNAi, rna interference; HKMT, histone lysine methyltransferase; SAM, s-adenosyl methionine; ATP, adenosine triphosphate; HAT, histone acetyltransferases; HAT, histone acetyltransferase

Introduction

Eukaryotic DNA is packaged into a macromolecular structure called chromatin by wrapping 147 base pairs of naked DNA around the histone octamer containing two copies of each core histone H2A, H2B, H3 and H4.[1] With the addition of linker histone H1 that binds to the nucleosome at the DNA entry-exit point, protecting the DNA linking adjacent nucleosomes, further compaction and condensation is achieved.[2] In order to facilitate cellular functions such as replication, transcription and DNA repair, the compaction of DNA is carried out in a way that gives rise to two structurally and functionally distinct chromosomal domains; namely euchromatin, representing the transcriptionally active, loosely packaged and gene-rich regions and the highly condensed and gene-poor heterochromatin.[3] The transition between euchromatin and heterochromatin is largely influenced by mechanisms involving DNA methylation, non-coding RNAs and RNA interference (RNAi), DNA replication-independent incorporation of histone variants and histone post-translational modifications (Figure 1).
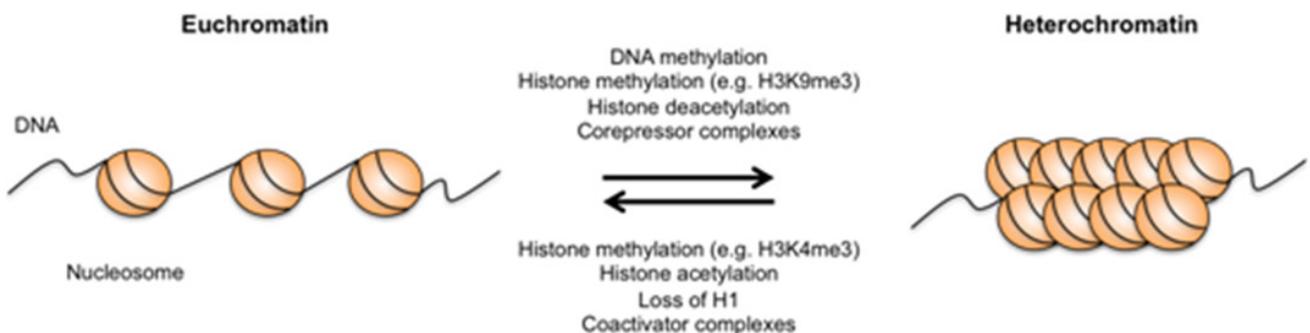

Figure 1 The conformational transition between euchromatin and heterochromatin.

Histones are tripartite proteins that are composed of a globular domain and unstructured N- or C-terminal tails that are subjected to several covalent modifications such as methylation, acetylation, phosphorylation as well as addition of large groups like ubiquitin and ADP-ribose.[4] The field of histone post-translational modifications (PTMs) is growing with many new sites of modifications and their modifiers being identified. All these efforts are put together to gain a better understanding of how histone PTMs modulate chromatin function. As suggested by the "histone code hypothesis", distributions of histone PTMs form a signature that is indicative of the chromatin state of a given loci.[5,6] Euchromatin is generally associated with high levels of histone acetylation. H3K9ac and H4K16ac are found at the promoters of actively transcribed genes while H3K27ac is enriched at enhancers together with another histone modification H3K4me1.[7,8] Di- and tri-methylations of histone H3 at K4 are modifications which are found in close proximity to active promoters.[9] H3K36me3 displays a distinct distribution pattern; it has the highest level at the 3'-end of an active gene and it decreases throughout the gene body.[10]

On the other hand, constitutive heterochromatin is enriched in repressive marks such as H3K9me3 and H4K20me3 which are deposited in mammals by Suv39-H1/2 and Suv4-20H1/2 respectively.[11,12] The characteristic mark of facultative heterochromatin is H3K27me3. Polycomb repressive complex 2 (PRC2) methylates histone H3 at K27, both at promoters and gene bodies, via its catalytic subunit EZH1/2.[13] After its establishment, H3K27me3 recruits PRC1 complex which ubiquitylates histone H2A at K119, further compacting the chromatin and locking the repressed state.[14,15] This review will focus only on 2 major types of histone modifications, namely histone methylation and phosphorylation; others will be discussed elsewhere.

Histone methylation

Methylation of histones is one of the most prominent histone PTMs, which is far more studied as N-methylation of lysine (mono-, di- or tri-methylated) and arginine (mono-, symmetrically or asymmetrically di-methylated) residues.[16] Recent studies identified many other amino acids to be methylated such as glutamine,[17] aspartic acid[18] and proline. The addition of the methyl group(s) is catalyzed by histone methyltransferases (HKMTs for lysine and PRMTs for arginine) that utilize SAM (S-adenosyl methionine) as the methyl-group donor. Majority of lysine methyltransferases contain a so called SET-domain that is required for the catalytic activity of the enzyme. More recently, enzymes that remove the methyl group (demethylases) have also been described, suggesting methylation as a dynamic mark.[19]

Unlike acetylation or phosphorylation, methylation of a histone does not result in alterations in charge. This is one reason why methylations could be both activating and repressing marks depending on the site and the degree. For instance, H3K4me1-2-3 is typically found at active transcription sites, whereas H3K9me2-3 and H3K27me2-3 are marks for heterochromatin and repressed gene state.[20] In contrast, mono-methylation of histone H3 at lysine 9 is linked with transcriptional activity.[21] Furthermore, bivalent genes harbor both H3K27me3 and H3K4me marks, which keep the genes in a "poised" state for transcription.[22] In addition, histones are methylated at various other lysine residues; H3 at K36, K56, K64, K79, H4 at K20 and H2B at K5.[20]

Arginine methylation has also been implicated in both transcriptional activation and repression. Some of the best characterized sites of arginine methylation are on histone H3; R2, R17 and R26 that are methylated by PRMT4/CARM1 and are active marks.[23] Histone H4 can be methylated at R3 either by PRMT1 or PRMT5 with different outcomes, where PRMT1 acts as a transcriptional activator while PRMT5 represses transcription.[24]

Histone phosphorylation

Histones are phosphorylated mainly on serine, threonine, tyrosine as well as much less studied sites such as arginine, histidine and lysine. Phosphate groups are added to and removed from the target histone residue by histone kinases and phosphatases respectively. The transfer of a phosphate group from ATP to the hydroxyl group of the amino acid side chain introduces a negative charge, which can affect electrostatic interactions within chromatin.[16] In line with this, histone phosphorylations play important roles in chromatin-related processes. Upon DNA-damage, the H2A variant H2A.X is phosphorylated at serine 139 by DNA-dependent protein kinases (ATR/ATM), forming so-called γH2A.X foci, which can extend for up to several megabases in mammals.[25,26] This H2A.XS139 phosphorylation facilitates the recruitment of the DNA damage repair machinery, as well as chromatin remodelers such as INO80 and SWR1.[27] γH2A.X signaling is often associated with a relaxed chromatin conformation, which makes the break site more accessible for DNA repair proteins.[28] Phosphorylations of H3 at serine 10 and 28, threonine 6 and 11 and H2B at serine 32 are associated with transcriptional regulation.[29] Furthermore, H3 N-terminal tail phosphorylations have been implicated in chromatin condensation and associated with cell division, among which serine 10 phosphorylation has been identified as a hallmark of mitosis and meiosis.[30,31]

Discussion

There are two major ways of how histone PTMs affect transcriptional regulation. Firstly, histone PTMs themselves may play a direct role in changing the chromatin structure or dynamics. For example, acetylation of a lysine neutralizes its positive charge and reduces the affinity of positively charged histone protein to the negatively charged DNA, thereby loosening up the chromatin, and is often associated with a more open chromatin conformation.[32] As a second –mutually not exclusive- mechanism, histone PTMs can act as signals to be recognized by "readers" which could be chromatin remodelers, histone acetyltransferases, histone methyltransferases or transcriptional co-activators that can translate these modifications in e.g. transcriptional output.[33] These readers contain evolutionarily conserved domains recognizing specific histone PTMs; such as bromodomains that are specific for acetyl-lysines and chromodomains for methyl-lysines.[34] They often are found in protein complexes with enzymatic activity to further modify the chromatin. For example, H3K27me, a repressive mark, recruits polycomb group proteins that are associated with another repressive mark, H2AK119ub.[35] On the other hand, histone PTMs can also exert their effect by blocking the docking sites of reader proteins and inhibiting their binding. For instance, H3S10P inhibits heterochromatin protein 1 (HP1) from binding to H3K9me.[36]

Many recent studies point out that there are numerous potential driver mutations within genes encoding for chromatin modifiers and perturbations in their regulation that result in carcinogenesis.[37] The alterations in the expression levels and/or functionality of these epigenetic players are most of the time advantageous for the cancer cell to grow and proliferate. These recent developments in dissecting the epigenetic basis of diseases such as cancer have opened a new avenue for researchers for epigenetic therapy. Specifically, misregulation of histone acetyltransferases (HATs) and histone deacetylases (HDACs) has been implicated in many cancers and first HDAC inhibitors has already been started to be used in patient treatment.[38] Likewise, inhibitors against poly (ADP ribose) polymerase 1 (PARP1), which is crucial for DNA repair and often found to help cancer cells overcome DNA-damage check points, are being tested against breast cancer in clinical trials.[39]

Conclusion

The growing evidence for the importance of post-translational modifications of histones in regulation of chromatin structure, dynamics, and function has attracted more attention to the field in recent years. However, we are still far away from having a complete map of all histone PTMs concerning novel modification sites as well as novel types of PTMs. To understand the multiple mechanisms how PTMs regulate chromatin function, it will be key to identify new histone posttranslational modifications and their modifiers. Therefore, future studies will shed light on the roles of histones beyond being structural components of chromatin and contribute to our current understanding of epigenetic regulation.

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Conflict of interest

The author declares no conflict of interest.

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