Histone Post-Translational Modifications in a Mitotic Chromosome

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During mitosis, many cellular structures are organized to segregate the replicated genome to the daughter cells. Chromatin is condensed to shape a mitotic chromosome. A multiprotein complex known as kinetochore is organized on a specific region of each chromosome, the centromere, which is defined by the presence of a histone H3 variant called CENP-A. The cytoskeleton is re-arranged to give rise to the mitotic spindle that binds to kinetochores and leads to the movement of chromosomes. How chromatin regulates different activities during mitosis is not well known. The role of histone post-translational modifications (HPTMs) in mitosis has been recently revealed. Specific HPTMs participate in local compaction during chromosome condensation. On the other hand, HPTMs are involved in CENP-A incorporation in the centromere region, an essential activity to maintain centromere identity. HPTMs also participate in the formation of regulatory protein complexes, such as the chromosomal passenger complex (CPC) and the spindle assembly checkpoint (SAC).

histones mitosis centromere kinetochore chromosome condensation nickel arsenic

1. Introduction

In eukaryotic cells, the DNA is bound to histone and non-histone proteins in a complex known as chromatin. In total, 147 base pairs of DNA are wrapped on a histone octamer formed by two copies of each of the core histones (H2A, H2B, H3, and H4). This unit is known as a nucleosome. Between nucleosomes, there are stretches of DNA bound to the linker histone H1 [1]. Core histones are constituted by a largely alpha-helical C-terminal domain, which is involved in the formation of the octamer and the DNA binding. The N-terminal region of core histones is organized in an unstructured tail. These tails and the C-terminal of H2A are the sites where most post-translational modifications are found [1][2]. Histones, like other proteins, can be modified in specific residues with the addition of different molecules; they can be acetylated, methylated, phosphorylated, and ubiquitinated, among other modifications. These modifications can change their affinity for DNA or can be “read” by other proteins and recruit specific factors to the nucleosome. Lysine acetylation was the first HPTM described. It opens condensed chromatin by promoting a charge neutralization in histones. Acetylated histones form a more relaxed chromatin which facilitates the recruitment of transcription machinery. Moreover, lysine acetylation is recognized by the bromodomain of several proteins that regulate gene expression. Lysine acetylation is also involved in DNA repair.

This mark is deposited by the histone acetyltransferases (HATs) and removed by the histone deacetylases (HDACs) [3][4].

Histone lysines and arginines can be methylated by enzymes that use S-adenosyl-L-methionine as a methyl donor. Lysines can be mono-, di-, or trimethylated, while arginines can be mono- or dimethylated. The role of lysine methylation in transcriptional regulation is well known. Lysine methylation is “read” by chromodomain-containing proteins, which can promote or repress transcription [5]. Lysine methylation is removed by lysine-specific demethylases (LSDs) or members of the Jumonji family of demethylases. On the other hand, the arginine methylation of histones is also associated with the regulation of gene expression [2]. The effect of histone methylation can differ depending on the position of the methylated residue and its level (mono-, di-, or trimethylated) [6][7]. Histone phosphorylation is an important mark for the DNA damage response (DDR). Histone phosphorylation is also associated with transcription regulation [2][8]. Finally, histone ubiquitination is another mark that has been associated with transcription regulation and DDR [9]. It has been proposed that histone modifications in the same histone tail or nearby tails from different histones can constitute a “code” that is interpreted to perform different functions in chromatin. Although the regulation of gene expression and DDR using histone HPTMs has been extensively studied, the role of histone PTMs in chromosome segregation has recently been revealed.

In addition to transcriptional regulation and DNA repair, HPTMs can play other structural and functional roles along the cell cycle. Particularly in mitosis, HPTMs are involved into the chromatin condensation, forming visible chromosomes under the microscope. Chromosome condensation is necessary to facilitate the transport and separation of genetic material to daughter cells. In this process, chromatin reduces its length by up to four orders of magnitude, significantly modifying its structure and physical properties [10]. Each chromosome harbors a region known as centromere, whose identity is defined by the presence of the distinctive H3 histone variant CENP-A, as well as several accompanying HPTMs [11]. The centromere is important because a multiprotein complex known as kinetochore is assembled onto that region, and it binds microtubules to align the chromosomes [12]. In addition, specific HPTMs also regulate the spindle assembly checkpoint (SAC) and the activity of the chromosomal passenger complex (CPC). The SAC checks the union between microtubules and kinetochores and stops mitosis until all chromosomes are attached to microtubules from the mitotic spindle. On the other hand, the CPC corrects kinetochore–microtubule attachment errors and participates in the contractile ring formation during cytokinesis [13][14]. Chromatin and specific HPTMs are involved in several of these processes during mitosis.

Remarkably, HPTMs are not only modified by cellular intrinsic factors but also by extrinsic environmental factors. For example, environmental pollutants can also modify HPTMs and disturb some of the mechanisms they are involved in [15]. Chromosome segregation is one potential mechanism that can be disturbed by environmental pollutants since histone PTMs are involved in its regulation.

2. Environmental Factors, Histone Post-Translational Modifications, and Genome Maintenance

The researchers reviewed that certain HPTMs play an essential role in proper chromosome condensation and centromere function during mitosis. Therefore, the abnormal alteration of these HPTMs or their regulators brings upon the cell severe consequences that can, in some cases, lead to genomic instability. Moreover, it is known that HPTMs and histone variants are regulated by intra and extracellular factors and by environmental factors. Consequently, the environment is also implicated in chromatin organization, gene expression, chromosome segregation, and a rise in genomic aberrations [16]. Here, the researchers list some environmental factors that can modify histone marks related to chromosome structures important in mitosis.

Arsenic is a pollutant metalloid widely distributed in nature and ubiquitous in soil, water, and air. Humans are chronically exposed to arsenic compounds through contaminated food and drinking water [17][18]. In nature, it can be found in organic or inorganic form, with the latter being the most toxic. The metabolism of inorganic arsenic gives rise to different methylated forms, of which dimethylarsinous acid (DMAIII) and monomethylarsonous acid (MMAIII) are the most toxic in vitro studies [19][20]. Arsenic has multiple cellular effects; it inhibits DNA repair, increases cellular oxidative stress, promotes apoptosis, provokes mitotic alterations, and modifies epigenetic marks [21]. It has been shown that arsenic causes an increase in mitosis length, the formation of chromosomal lags, and the generation of aneuploidies in vitro [17][22][23]. The consequences of cellular exposure to arsenic depend on its chemical species and dose, e.g., sodium arsenite in high doses (greater than 5 micromolar) causes cell death after mitotic arrest instead of only delaying mitosis [17][23].

Although some of the effects of arsenic in mitosis have been associated with its binding to tubulin [24], the formation of the mitotic spindle [25], and the inhibition of proteins such as Plk1 [17], changes in histone marks could alter the mechanisms of condensation and centromere functioning, provoking the mitotic alterations observed in arsenic-treated cells. For example, Suzuki et al. showed that treatment with DMAIII results in the increased phosphorylation of H3S10, a mark associated with chromosome condensation. Furthermore, treatment with DMAIII affected the CPC's proper location and chromosome segregation [26]. Thus, alteration of this histone mark could inhibit adequate chromosome condensation and segregation. As previously mentioned, the phosphorylation of H3S10 allows the recruitment of Hst2p, which deacetylates the H4K16 residue by promoting chromosome compaction. Arsenic treatment decreases the overall levels of histone acetylation [27][28][29] and H4K16ac by binding to and inhibiting hMOF (the histone acetylase enzyme responsible for the acetylation of H4K16) [28][30]. Because this alteration was evaluated in the interphase, it will be relevant to determine whether arsenic also modifies the acetylation of H4K16 in mitosis and the consequences it may have on chromosome segregation. As already stated, the presence of H3K4me2 and H2Bub1 modifications are significant for CENP-A recruitment and centromere maintenance. In this regard, it has been shown that cellular exposure to arsenic causes an increase in global H3K4me2 and H3K4me3 [31][32][33]. Although the centromeric region has a significant level of H3K4me2, it also has low levels of H3K4me3, so the increase in the latter mark could modify the structure of centromeric chromatin and alter the recruitment of CENP-A.

On the other hand, treatment with arsenic for long periods has the opposite effect, causing a decrease in both H3K4me2 and H3K4me3, the latter being associated with an increase in KDM5 (a histone demethylase) [34]. In C. elegans, it was shown that arsenic treatment promotes a transgenerational reduction in H3K2me2 levels

associated with a decrease in spr-5 expression (which codes for a histone demethylase that removes the H3K4me2 mark) [31]. On the other hand, arsenic can bind to the RNF20 protein (the enzyme that generates histone H2B ubiquitination) and inhibit its function, causing a decrease in H2Bub1 levels [35]. As the overall modification of H3K4me2 and H2Bub1 by exposure to arsenic has been evaluated, it will be relevant to define whether these alterations are also present at the centromeric level. It is also essential to determine whether these changes are responsible for specific defects during chromosome segregation.

Nickel (Ni) is a metal found in the environment and originated from the erosion of rocks and volcanic origin. Most of the Ni has an anthropogenic origin due to fossil fuels and industrial processes [36]. Ni is deposited in the soil and is also found in the atmosphere. It can be found as elemental nickel (Ni), nickel oxide (NiO), nickel chloride (NiCl2), and nickel sulfate (NiSO4), among others [37]. Different studies have shown that exposure to Ni causes alterations in chromosome segregation. The treatment of cell cultures with Ni promotes an increase in cells with kinetochore-positive micronuclei [37][38][39]. Moreover, an increase in aneuploid cells and alterations during anaphase have been found after treatment with Ni compounds [38][40].

In various models, it has been shown that Ni can modify histone marks, some of which may be related to mitotic chromosome formation and functioning. In vitro assays have demonstrated that Ni promotes chromatin condensation independently of the cellular machinery. Moreover, Ni treatment is associated with DNA methylation and gene silencing [41][42][43]. As previously mentioned, H3S10ph is an important mark for chromosome compaction. Cells treated with Ni increase the overall levels of H3S10ph [44]. However, the increase in H3S10ph was observed only at the interphase, so it is unclear whether this alteration can affect mitotic chromosome compaction. The role of H3S10ph in the compaction of chromosomes is also associated with the deacetylation of histone H4. Ni diminishes global acetylation of H4 [45][46]. It has been proposed that the inhibition of H4ac is due to the formation of ROS caused by Ni [47]. However, it has also been associated with the direct binding of Ni to histone H4, which prevents its binding to HATs [48]. Moreover, Ni has been shown to decrease local acetylation of H3 and increase H3K9me2 and H3K9me [49][50]. Finally, Ni also increases global levels of H2Aub and H2Bub by inhibiting the deubiquitination of both histones [51]. In most of these studies, changes in histone marks have been studied globally, so it will be relevant to define whether these alterations are present in specific loci and if Ni alters particular marks. It will also be essential to know if modifications in histone marks are associated with defects in segregation caused by Ni and if these marks are specifically modified during mitosis.

In addition to Ni, other metals can modify histone marks and chromosome segregation. Cadmium, for example, causes the formation of aneuploidies in vitro and changes the methylation patterns of DNA and histones [52]. Cadmium also increases H3K4me3 and H3K9Me2 by inhibiting the demethylases that remove these marks [53].

On the other hand, ambient particulate matter (PM) can modify both histone marks and chromosome segregation. Exposure to soil and road dust decreased the expression of Suv39h1 (a histone methyltransferase responsible for H3K9 methylation) with a concomitant increase in centromeric satellite DNA expression. As previously mentioned, the expression of these sequences is tightly associated with CENP-A incorporation. Accordingly, the authors of this work observed chromosome aberrations under soil dust exposure in vitro [54]. Airborne particulate matter also

modifies histone mark patterns. PM10 (particles with an aerodynamic diameter smaller than 10 μm) exposure promotes acetylation of histone H4 by increasing HAT activity [55]. Moreover, PM10-exposed human cells showed an increase in micronucleated and trinucleated cells [56]. However, particles obtained from different regions or different times of the year may have a different composition. The same PM10 sample must be used for experiments to determine whether PM10 exposure can alter histone marks and chromosome segregation.

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