Histone modifications under environmental stress

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Abstract: Chromatin is a highly organized complex consisting of DNA and chromosomal proteins, which undergo dynamic changes. Histones are basic chromosomal proteins, extremely conserved throughout evolution, which are divided into 5 types: H1, H2A, H2B, H3, and H4. Histone proteins may undergo numerous post-translation modifications, which play a significant role in chromatin structure and function. Various environmental factors cause changes in chromatin structure, gene expression, and protein pattern. Here, we present histone modifications that occur under various environmental stresses.

Keywords: heavy metals, histone, histone modifications, environmental stress

INTRODUCTION

Histones are alkaline proteins, associated with nuclear DNA and compacted to form chromatin. Histones were found as major protein components of cellular nuclei already at the end of the 19th century (KOSSEL 1884). Five types of histones are distinguished: H2A, H2B, H3, H4 (named core histones), and H1 (called linker histone). Two different domains can be distinguished in core histones. The first one is a globular domain containing the histone-fold motif involved in interactions between histone proteins. The second domain is the N-terminal tail of H3 and H4, or N- and C-terminal tails of H1, H2A and H2B (KALLIN & ZHANG 2004). The tails of histones are subject to dynamic and covalent changes by post-translational modifications, such as: acetylation, methylation, phosphorylation, ubiquitination, glycosylation, carbonylation, ADP-ribosylation, sumoylation, and biotination (JENUWEIN & ALLIS 2001, TURNER 2002, KALLIN & ZHANG 2004). Most of the modifications occur on the N-terminal tails of histones. The various modifications not only have structural functions, but they also play a significant role in several valid biological processes and probably induce regulatory signals (RAMAKRISHNAN 1997, STRAHL & ALLIS 2000). All of the post-translation modifications can cause structural and functional changes in chromatin (JENUWEIN & ALLIS 2001, TURNER 2002) and regulate...
some biological processes, including transcription, DNA repair, and apoptosis (FERNANDEZ-CAPETILLO et al. 2004a, KIMURA 2005).

Histone proteins are susceptible to acid extraction and most of them have been conserved during evolution. Particularly strongly conserved are core histones (H2A, H2B, H3, H4), whereas linker histone H1 is less conserved than others (DELANGE et al. 1969). Despite the high degree of evolutionary similarity, some of the histone proteins have different isoforms in various organisms. Research conducted over the past few years has revealed several interesting functions and properties of histones. It is therefore accepted that the histone modifications are part of a much more universal protein code that governs interactions of proteins with other molecules. However, most of the studies concerned yeast and animals, while still little is known about the specific functions of histone modifications in plants.

Heavy metals, UV radiation and salinity are examples of environmental stressors that can cause damages in cells. Furthermore, latest studies suggest that histones may participate in the reaction of cells to heavy metals and other environmental stressors. Toxic environmental factors cause several unfavourable morphological, physiological and biochemical changes in eukaryotic organisms. In plants, environmental factors cause, among other reactions, the inhibition of development, death of groups of cells, tissues, organs or even of the whole organism. The symptoms of phytotoxicity involve the inhibition of cell elongation, differentiation and necrosis. Environmental stressors affect gene expression on different levels and may cause DNA damage. DNA damage can lead to formation of a tumour or directly to the apoptosis pathway in the case of mammalian cells (ZHOU & ELLEDGE 2000). Mechanisms of genotoxic signal perception and programmed cell death (PCD) are still not sufficiently elucidated in plants. Several lines of evidence suggest that histone modifications may play a role in cell response to environmental stresses. This review is aimed to summarize all the available results of research on this topic.

**ACETYLATION**

The existence of histone acetylation and methylation was discovered by Vincent Allfrey and his associates over 40 years ago (ALLFREY et al. 1964).

The nucleosome core histones undergo reversible acetylation in selected lysine residues, located in N-terminal tails of histones. In a nucleosome there are 26 different sites, which can be acetylated (SPENCER & DA VIE 1999). The predominant positions for acetylation are for example: lysine 9, 14, 18, 23 of H3; lysine 5, 8, 12, 16, 20 of H4; lysine 5, 9 of H2A, and lysine 5, 12, 15, 20 of H2B (TURNER 2002, KALLIN & ZHANG 2004).

The reversible histone acetylation is catalysed by 2 types of enzymes: histone acetyltransferase (HAT, which uses acetyl-CoA as a cosubstrate) or histone deacetylase (HDAC) (GRAESSLE et al. 2001, CARROZZA et al. 2003, DE RUIJTER et al. 2003, TIAN et al. 2005). They belong to separate protein families and are associated with large multisubunit complexes (OGRYZKO 2001). Recent data showed that HATs fulfil simultaneously the function of transcription coactivators, while HDACs are corepressors (KALLIN & ZHANG 2004). We can distinguish 4 families of HATs: (1) the
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GNAT-MYST family; (2) the p300/CBP coactivator family; (3) the TAF\textsubscript{II}250-related family; and (4) the nuclear receptor coactivator family.

The relationship between histone modifications and gene expression has been documented (BROWNELL et al. 1996, TAUNTON et al. 1996). HATs and HDACs modify not only histones but also many non-histone regulatory and structural proteins, such as: p53, retinoblastoma protein (pRb), tubuline, and c-Myc (GU & ROEDER 1997, CHAN et al. 2001, VEROORTS et al. 2003). The p300/CBP proteins can acetylate all core histones but also numerous transcription factors, such as p53 and GATA-1. For example, pCAF protein (p300/CBP-associated factor) plays a role in modulation of p53 activity in response to UV-induced DNA damage. The protein acetylates the C-terminal tail of p53 protein, which causes binding to specific DNA sequences (LIU et al. 1999, CHAN & LATANGUE 2001).

The acetylation of histone proteins plays an important role in the transcription process. Acetylases could activate transcription by enhancing the initiation and elongation stages. Generally, gene activation by histone acetylation leads to a relaxation of chromatin structure (EBERHARTER & BECKER 2002, KURDISTANI & GRUNSTEIN 2003, KALLIN & ZHANG 2004).

Acetylation of lysine residues in the N-terminal tails of histones is associated with actively transcribed genes (HEBBES et al. 1988). Heavy metals, such as nickel and copper, inhibit histone acetylation via the action of HAT, and this is associated with silencing of gene expression (YAN et al. 2003, KANG et al. 2004, MOGGS & ORPHANIDES 2004). The inhibitory effect of nickel on acetylation of lysine residues of histone H4 occurs by binding of metal near histidine 18, located within the conserved sequence of the N-terminal tail of histone H4 (ZORODDU et al. 2000, ZORODDU et al. 2002). Nickel also suppressed the acetylation of H2B (GOLEBIOWSKI & KASPRZAK 2005). Additionally, at nontoxic levels, nickel decreased the levels of histone H4 acetylation in both yeast and mammalian cells, affecting only lysine 12 in mammalian cells and 4 lysine residues in yeast (BRODAY et al. 2000). A loss of histone H4 acetylation may be coupled with DNA methylation in inactivation of gene expression in mammalian cells exposed to nickel (BRODAY et al. 2000, NG & BIRD 1999). The inhibitory effect of nickel has been confirmed for all core histones. Nickel exposure can also alter chromatin structure through the truncation of histone H2A via cleavage of an octapeptide from its C-terminus (KARACZYN et al. 2003, MOGGS & ORPHANIDES 2004). Inhibition of transcription of specific genes (aryl-hydrocarbon-inducible genes) in mammalian cells has been observed in the case of chromium (WEI et al. 2004). Histone acetylation induced in salt stress may signal a change in transcriptional activity at the chromatin level (WATERBORG et al. 1989). It has been proved that post-synthesis acetylation of histone proteins is associated with chromatin activation and gene transcription in eukaryotes.

In contrast to acetylation, deacetylation of histone proteins leads to repressed chromatin state and gene silencing. Mammalian histones are deacetylated by large complexes containing various proteins, such as mSin3A and NuRD complexes (KNOEPFLE & EISENMAN 1999). The deacetylase complexes show activity in the presence of several acetylated proteins, HMG (high mobility group proteins) and transcription factors.
METHYLATION

The methylation of histones mainly occurs in histone tails, on arginine and lysine residues. The modification of histones by lysine and arginine residue methylation has been shown only in histones H3 and H4 (Zhang & Reinberg 2001, Martin & Zhang 2005). This process is catalysed by various enzymes belonging to the PRMT family (catalysing arginine methylation) or by SET-DOMAIN-containing proteins (histone lysine methyltransferases – HMTases, such as SUV39H1), or by non-SET-DOMAIN proteins DOT1/DOTL1 (Zhang & Reinberg 2001, Reyes et al. 2002, Wagner 2003, Bannister & Kouzarides 2005).

Recently several specific sites of methylation have been reported: 5 lysine residues of H3 (K4, 9, 27, 36, and K79, the last one located inside the globular domain), lysine 20 of H4, 2 arginine residues of H3 (R17, 26), and arginine 3 of H4 (Kallin & Zhang 2004, Loidl 2004, Tariq & Paszkowski 2004).

Site-specific methylation fulfils an important role in many biological processes (Feng et al. 2002). Methylation can signal either activation or repression of gene expression. The final effect of methylation is site-dependent (Turner 2002, Martin & Zhang 2005). For example, the methylation of lysine 4, 36, 79 of H3 is correlated with gene activation, but methylation of lysine 9, 27 of H3 and lysine 20 of H4 usually causes gene silencing (Fischle et al. 2003, Kallin & Zhang 2004). Furthermore, a recent study has shown an influence of a heavy metal on the histone pattern, because increased dimethylation of lysine 9 of H3 is induced by nickel chloride (Chen et al. 2006, Ke et al. 2006).

PHOSPHORYLATION

The modification of histones by phosphorylation has been observed in all classes of histones. This modification occurs on serine and threonine residues (Kallin & Zhang 2004). Recently, 4 sites of serine residue phosphorylation have been localized on serine 10 and 28 of H3; serine 1 of H4, serine 1 of H2A, serine 139 of H2AX, and serine 14 of H2B. It is well known that phosphorylation of histones is cell-cycle-dependent, with the highest level of this modification occurring in the M phase of the cycle (Schroeder-Reiter et al. 2003, Kallin & Zhang 2004).

Phosphorylation of serine 10 and 28 of H3 takes part in the establishment of transcriptional competence of mammalian immediate-early response genes. Phosphorylation of histone H3 (at positions of serine 10 and 28) increases under osmotic stress and seems to be a response to various environmental stresses (Burkhart et al. 2007). Furthermore, this process occurs during DNA damage and apoptosis (Kallin & Zhang 2004). Ionizing radiation causes a fast phosphorylation of serine 139 in H2AX (a H2A histone variant) in mammalian cells. The phosphorylated form of H2AX has been found in the proximity of DNA double-strand breaks (DSBs) (Rogakou et al. 1999, Khanna & Jackson 2001, Fernandez-Capetillo et al. 2004b, Van Attekum & Gasser 2005). Research on yeast suggests participation of histone H2B in repair of UV-induced DNA damage (Martini et al. 2002). It was discovered simultaneously that phosphorylation of H2AX (at the position of serine 139) is a DNA damage indicator, but phosphorylation of H2B (at the position of serine 14) is an
apoptosis indicator (CHEUNG et al. 2003, FERNANDEZ-CAPETILLO et al. 2004a). Various heavy metals ions can also change the phosphorylation status of histone proteins. Rapid phosphorylation of serine 10 on histone H3 occurs in response to arsenite treatment (HE et al. 2003, MOGGS & ORPHANIDES 2004). Phosphorylation also facilitates a rapid alteration in chromatin structure within the region containing the mammalian stress response genes (CLAYTON & MAHADEVAN 2003, MOGGS & ORPHANIDES 2003). Although the described metal-induced inhibition of histone H4 acetylation as well as histone H3 phosphorylation have not been described in plants, the presence of respective amino acid residues in plant histones (histidine 18 in histone H4 and serine 10 in histone H3) make these processes possible.

UBIQUITINATION

Histones H2A and H2B can also be reversibly ubiquitinated. Ubiquitin is a conserved protein, which is composed of 76 amino acids. Ubiquitination occurs on the specific lysine residues, located at position 119 of H2A and position 120 of H2B. About 10% of H2A and 2% of H2B are ubiquitinated in higher eukaryotes (KALLIN & ZHANG 2004). H2B ubiquitination has long been linked to transcriptionally active genes. A recent study has shown that nickel induces changes in ubiquitination level of 2 core histones: H2A and H2B (KARACZYN et al. 2006). KARACZYN et al. (2006) suggest that the changes in H2B ubiquitination are adverse effects of nickel on gene expression and DNA repair, which may assist in tumour transformation of mammalian cells. Other authors, KE et al. (2006), reported that exposure to soluble nickel compounds leads to a substantial increase in the ubiquitination of H2A and H2B.

OTHER EFFECTS OF ENVIRONMENTAL FACTORS ON HISTONE PROTEINS

It has been shown that metals can change either the transcript or protein level of some histones. Cadmium treatment of soybean cells induces the histone H2B protein and respective mRNA accumulation (SOBKOWIAK & DECKERT 2006, PAWLAK et al. 2007), whereas aluminium treatment of Oryza sativa plants causes an induction of histone H4 transcript (MAO et al. 2004) The appearance of histone H2B protein during cadmium treatment might be correlated with cadmium-induced DNA damage and apoptosis (FOJTOVA & KOVARIK 2000, WU et al. 2002, SOBKOWIAK & DECKERT 2004). An increased level of histone H2B is required in Saccharomyces cerevisiae for repair of UV-induced DNA damage (MARTINI et al. 2002). The same role may be played by histone H2B in plant cells exposed to genotoxic stress factors, such as heavy metals. There is also a report concerning other effects of heavy metal on histones, which shows that exposure of cells to nickel results in truncation of histones H2A and H2B, and elimination of some modification sites (KARACZYN et al. 2005).

Up to now we still do not have complete information about the role of histones in reaction to environmental stress. We know little about heavy metal stress and about radiation stress, whereas reactions at the histone level and histone modification by various stressors are still unknown or poorly studied. Although progress in this field has been impressive, many questions remain to be addressed.
REFERENCES


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