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Review

Sensing core histone phosphorylation — A matter of perfect timing ☆

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ABSTRACT

Systematic analysis of histone modifications has revealed a plethora of posttranslational modifications that mediate changes in chromatin structure and gene expression. Histone phosphorylation is a transient histone modification that becomes induced by extracellular signals, DNA damage or entry into mitosis. Importantly, phosphorylation of histone proteins does lead not only to the binding of specific reader proteins but also to changes in the affinity for readers or writers of other histone modifications. This induces a cross-talk between different chromatin modifications that allows the spatio-temporal control of chromatin-associated events. In this review we will summarize the progress in our current knowledge of factors sensing reversible histone phosphorylation in different biological scenarios. This article is part of a Special Issue entitled: Molecular mechanisms of histone modification function.

1. Introduction

Eukaryotic DNA is organized in a complex with histone proteins as chromatin. The nucleosomal (and higher order) chromatin structure facilitates the packaging, organization and distribution of eukaryotic DNA but has a negative impact on several fundamental biological processes such as transcription, replication and DNA repair by restricting the accessibility for high molecular weight protein complexes. Posttranslational modification (PTM) of histones by acetylation, methylation, ubiquitination or phosphorylation has been shown to modulate the chromatin structure by changing protein–DNA or protein–protein interactions. Mass spectrometry analysis and application of modification-specific antibodies led to the identification of a large number of different PTM sites, located mostly not only at the N-terminal tails but also within the globular domains of histone proteins [1–4]. Some of these modifications such as histone methylation at K9 or K27 are more stable PTMs and are crucial for development, heterochromatic silencing and maintenance of cell identity [5]. Other modifications including histone acetylation and phosphorylation are transient and dynamic events [6,7] and constitute integral components of the chromatin signaling pathway [5]. PMTs of histones, alone or in combination, reflect specific biological events and chromatin states. Reader proteins with particular binding modules recognize specific histone marks and act together with associated complexes to orchestrate a variety of chromatin-associated processes such as transcriptional regulation, chromatin condensation or DNA damage repair [3].

Histone phosphorylation is targeted to serines (S), threonines (T) and tyrosines (Y) and its abundance can range from targeting a minute fraction of nucleosomes during the G0/G1 of the cell cycle [8] to association with most nucleosomes of the G2/M-phase chromatin [9]. Histone phosphorylation marks play an important role in the interpretation of combinatorial PTMs by components of the chromatin-based signaling machinery. In this review we will discuss the function of sensors of histone phosphorylation in the context of transcriptional regulation by extracellular signals, chromatin condensation during mitosis and DNA damage.

2. 14–3–3 proteins as readers of the H3S10ph mark

Activation of signaling cascades in response to stress, growth factors or immune stimulation ultimately results in the phosphorylation of many cellular targets including histone proteins. Although histone phosphorylation has been studied since the sixties of the last century, only few proteins directly binding this modification have been identified [10–13]. The discovery of members of the 14–3–3 family as the first selective phospho-histone interacting proteins with specificity for the H3S10ph mark has paved the way to understand the role of this modification in transcriptional activation [14]. 14–3–3 proteins constitute an abundant family of phosphoserine/phosphothreonine binding modules that homo- and heterodimerize to associate with other factors to alter their conformation, cellular localization, enzymatic activity or the ability to interact with other partners [15]. 14–3–3 proteins are highly conserved and are able to complement for the loss of their homologues even when expressed in distantly related species [16]. The mammalian 14–3–3 family comprises seven members that have been

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demonstrated to interact with 700 different factors [17], including many transcriptional regulators and chromatin-modifying proteins, such as the TATA-binding protein [18], p53 [19] and histone deacetylases [20]. In vitro pull down assays using synthetic peptides corresponding to the N-terminal tail of histone H3 phosphorylated at S10 and human nuclear extracts, followed by mass spectrometry, identified 14–3–3 isoforms as phospho-specific binding proteins [14,21,22]. Importantly, the affinity of 14–3–3 for the H3S10ph mark is increased when one of the neighboring lysine residues, K9 or K14 is acetylated [21,22]. Structural and biochemical studies have revealed the molecular bases of this phenomenon. First of all, the motif containing phosphorylated S10 at histone H3 does not match the known 14–3–3 consensus binding motifs, as it lacks the proline residue at the position P + 2 [15,23] (Fig. 1A). In agreement with this finding, H3G12P substitution significantly increased the affinity of 14–3–3 to the level observed for a phosphoacetylated H3S10phK14ac peptide in in vitro binding assays [23]. It has been therefore suggested that the presence of H3K14 acetylation counterbalances the lack of proline in the 14–3–3 binding motif. In recent molecular modeling approaches 14–3–3ζ has been shown to preferentially bind the H3S10phK14ac mark and additional acetylation of H3K9 favors binding of the mitogen-activated protein kinase phosphatase-1 (MKP1) to dephosphorylate S10 [24]. In this in silico analysis a preferential interaction of mitogen- and stress-activated kinase-1 (MSK1) with non-acetylated histone H3 compared to K9- and K14-acetylated H3. In summary these data indicate that combinatorial phosphorylation and acetylation of histone H3 modulate the affinity for readers and potentially also for erasers.

3. Link between histone phosphorylation and acetylation

Site-directed chromatin immunoprecipitation (ChIP) analysis using dual modification specific antibodies revealed the presence of the H3S10phK14ac mark at activated promoters in vivo [21,25–27]. This raises an important question about the mechanism underlying the simultaneous targeting of the two PTMs to the same histone H3 tail. Literature provides two models explaining this phenomenon. The first one implies that histone H3 phosphorylation and acetylation are spatially linked but independent processes and one of the PTMs is not required for the establishment of the other [8,28]. According to the alternative model, the co-existence of the two PTMs is the result of synergistically coupled recruitment of kinases and histone acetyltransferases. In agreement with this model, the activity of yeast histone acetyltransferases (Gcn5, PCAF and p300) towards K14 on H3 peptides was shown to be significantly higher when a peptide phosphorylated at S10 was used

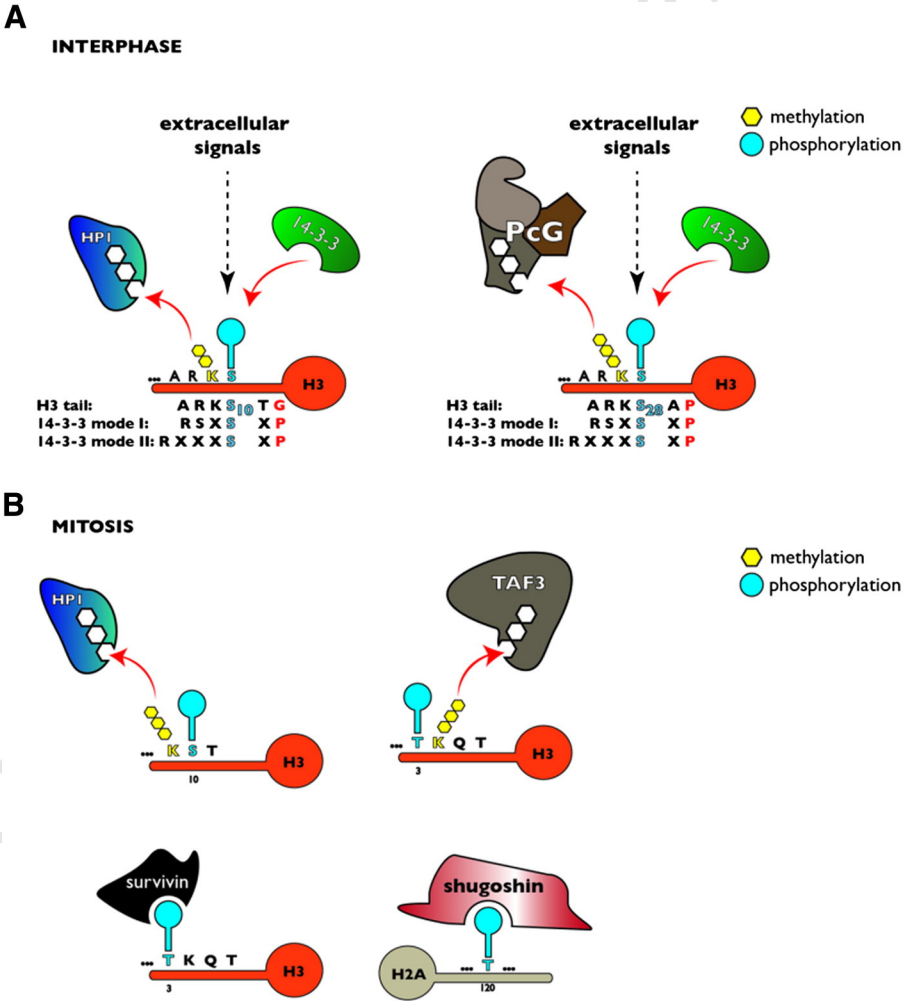

Fig. 1. Sensors of histone phosphorylation during interphase and mitosis. (A) The phospho-methyl switch during interphase: Signal-dependent phosphorylation of H3S10 or H3S28 triggers the dissociation of the repressive readers HP1 and PcG from the respective neighboring methylated lysine residues and recruitment of the reader 14–3–3 resulting in the transient activation of target genes. Sequence alignment of high affinity 14–3–3 consensus motifs of mode I and mode II with 14–3–3 binding sites within histone H3. The critical position at P + 2 (red residues) from the phosphorylated serines (blue residues) is occupied by glycine 12 for serine 10 and proline 30 for serine 28, respectively. (B) Redistribution of the chromosomal passenger complex (CPC) and transcriptional silencing during mitosis. Aurora B-mediated phosphorylation of H3S10 during mitosis leads to dissociation of HP1 from H3K9me3. CPC relocalization to the inner centromere is mediated by binding of survivin to H3T3Tph and interaction of borealin-associated shugoshins with phosphorylated H2AT120. H3T3 phosphorylation by haspin results in dissociation of TAF3 from trimethylated H3K4.

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