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Interphase H1 phosphorylation: Regulation and functions in chromatin☆

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ABSTRACT

Many metazoan cell types differentially express multiple non-allelic amino acid sequence variants of histone H1. Although early work revealed that H1 variants, collectively, are phosphorylated during interphase and mitosis, differences between individual H1 variants in the sites they possess for mitotic and interphase phosphorylation have been elucidated only relatively recently. Here, we review current knowledge on the regulation and function of interphase H1 phosphorylation, with a particular emphasis on how differences in interphase phosphorylation among the H1 variants of mammalian cells may enable them to have differential effects on transcription and other chromatin processes. This article is part of a Special Issue entitled: Histone H1, edited by Dr. Albert Jordan.
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1. Introduction

Linker or H1 histones are lysine, alanine and proline-rich proteins that bind both nucleosomal and linker DNA and facilitate higher order chromatin folding [1–3]. Many eukaryotes express multiple amino acid sequence variants of H1. Early biochemical analyses of cells derived from metazoan organisms suggested that H1 variants, collectively, are phosphorylated progressively during the G1, S and G2 portions of the cell cycle until the G2/M transition when rapid and transient phosphorylation to maximum levels coincides with chromosome condensation and mitosis [4]. This early work did not identify sites of phosphorylation or define possible differences in the patterns of interphase and mitotic phosphorylation between individual H1 variants. However, more recent analyses have revealed specific differences in interphase and mitotic phosphorylation between individual metazoan H1 variants. The mechanisms linking mitotic phosphorylation of H1 proteins with chromosome condensation remain enigmatic, but considerable progress has been made in investigating the nature and function of interphase phosphorylation of metazoan H1 variants. The evidence reviewed below suggests that differences in the genomic localization of individual H1 variants, together with differences in their patterns of interphase phosphorylation are significant factors in regulating gene expression.

2. The multiplicity of H1 variants in higher eukaryotes

The genomes of higher eukaryotes typically contain multiple single copy genes that encode non-allelic amino acid sequence variants of H1. *Caenorhabditis elegans* has eight, *Xenopus laevis* has five, chicken (*Gallus gallus*) has seven, while both mouse (*Mus musculus*) and human (*Homo sapiens*) have eleven [5,6]. Among the eleven H1 variants present in the human genome, the seven "somatic" variants, H1.X, H1.0, H1.1, H1.2, H1.3, H1.4 and H1.5, are differentially expressed in a wide variety of tissues. Five of these, H1.1, H1.2, H1.3, H1.4 and H1.5, are replication-dependent variants expressed predominantly during S-phase whose amino acid sequences are more conserved with one another compared to the remaining variants [5,6]. In contrast, amino acid sequence differences are more numerous in the replication-independent H1.0 and H1.X variants [5–8]. The most divergent of the eleven human H1 variants are selectively expressed in germline tissues. Three distinct H1 variants, H1t, H1T2 and H1LS1, replace somatic H1 variants during the extensive chromatin remodeling that occurs during spermatocyte differentiation [5,6,9–12]. H1oo, a novel homolog of the Xenopus B4/H1M linker histone, is expressed in mammalian oocytes. In mice, alternative splicing gives rises to two transcripts whose expression correlates with the onset of ooctye development from resting primordial follicles [13].

All metazoan H1 variants share a tripartite structure containing a central folded globular domain (GD, approx. 80 residues) flanked by a short N-terminal domain (NTD, approx. 13–40 residues) and a longer C-terminal domain (CTD, approx. 100–125 residues). The NTD and CTD are predominantly unfolded in solution in the absence of DNA, but behave like instrinsically disordered proteins in that their binding

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to DNA is coupled with folding to assume elements of conventional secondary structure [1,14–18] (see the review from the Suau lab in this issue). The amino acid sequence of the GD is highly conserved among the H1 variants of different species whereas more extensive differences in the NTD and CTD sequences define individual variants from one another within species, and these differences are often conserved in homologous variants of different species [5,6]. H1 variant-specific amino acid sequence differences in each of these domains are likely to be functionally significant. The role of the NTD in chromatin is poorly understood, but it appears to contribute to the affinity of H1 variants for chromatin and differences in NTD structure between H1 variants correlate with their differential chromatin binding properties [19,20]. As discussed below, differences in NTD interphase phosphorylation exist between H1 variants that may also be involved in conferring variant-specific functions. The structure and function of the GD has been studied extensively and we refer readers to recent reviews that deal with this topic [21] (also see reviews from the Suau lab and the Bednar lab in this issue). Although many details remain to be elucidated, several findings on GD function are pertinent to understanding how interphase phosphorylation may affect the functions of H1 variants differentially. Biochemical and structural analyses have demonstrated two different overall modes of H1 binding to nucleosomes, a symmetric mode in which the GD binds nucleosomal DNA at the particle dyad and interacts with similar amounts (approx. 10 bp) of both linker DNAs entering and exiting the particle [1,22,23], or an asymmetric mode in which the GD binds nucleosomal DNA off the dyad and binds different amounts of the linker DNAs entering and exiting the particle [24–30] (also see reviews from the Bednar lab and the Suau lab in this issue). The GDs of chicken H5 and the Xenopus ortholog, H1.0, bind on the dyad [23] while human H1.4 and *Drosophila* H1 prefer off-dyad binding [28,29]. These different modes of binding are likely to differ in their impact on higher order chromatin folding and nucleosome remodeling associated with transcription and other processes. It has been suggested that the preference for on-dyad versus off-dyad binding may be determined by the distribution of positively charged residues at a limited number of positions within the GD [23]. However, additional factors appear to be involved since even though the positive residues thought to be key for symmetric binding of GH5 and GH1.0 are conserved in human H1.1–H1.5, current evidence indicates that the GD of human H1.4 and mouse H1.2 binds in an asymmetric fashion [28,31], whereas that of mouse H1.5 appears to bind symmetrically [22]. Thus, even in the case of the somatic H1 variants (H1.1–H1.5), differences in chromatin binding mode by their GDs may combine with differences in interphase phosphorylation within their NTDs and CTDs to affect chromatin processes differentially. Evidence for phosphorylation at several non-cdk type sites within the GD has been described [32–34], but to the best of our knowledge the cell cycle dynamics and significance of these events have not been investigated. Despite their potential significance, they will not be considered further here. Below, we review recent evidence on the regulation and function of the relatively well characterized sites of NTD and CTD interphase phosphorylation that conspicuously distinguish individual H1 variants from one another and may be involved in conferring H1 variant-specific functions in transcription and other processes.

3. H1 phosphorylation in mammalian cells

Apart from the exceptions noted below (see H1 phosphorylation in other eukaryotes), H1 is phosphorylated progressively at multiple sites during cell cycle progression in many eukaryotes. The work reviewed below has revealed that phosphorylation sites in mammalian H1 variants can be classified according to their structure and the portions of the cell cycle in which they are phosphorylated. The majority of the known sites are S/T-P-X-Z motifs (where X = any residue and Z = a basic residue) preferred by cyclin-dependent kinases (cdks). In the case of mammalian H1 variants, cdk type sites in H1 variants that contain T as the phosphoacceptor (TPXZ) appear to be phosphorylated exclusively during mitosis whereas those containing S as the phosphoacceptor (SPXZ) can be phosphorylated during both interphase and mitosis. Thus, metazoans appear to phosphorylate H1 variants exclusively (or predominantly) at SPXZ sites during interphase.

Early analyses of H1 variant mixtures prepared from ^{32}P-orthophosphate-labeled synchronized cultures of Chinese hamster ovary cells (CHO) using Bio-Rex 70 chromatography detected phosphorylated H1 initially in late G1 phase, followed by progressively increasing levels during S phase and G2 phase before peaking transiently during mitosis [35,36]. Interphase H1 phosphorylation occurred preferentially on serines in the C-terminal fragment generated by N-bromosuccinimide (NBS) cleavage at the single tyrosine within the GD [36]. Additional threonine phosphorylation was found in both the N- and C-terminal NBS fragments during mitosis. These findings provided initial evidence that interphase and mitotic phosphorylation of H1 may occur at different sites. Analyses of synchronized HeLa S3 cells also indicated that H1 was phosphorylated progressively through the cell cycle and provided evidence suggesting that H1 variants possessed different numbers of sites for interphase and mitotic phosphorylation [37,38]. Subsequently, reverse phase HPLC (RP-HPLC) separation of individual H1 variants from synchronized mouse 3 T3 cells and rat C6 glioma cells followed by the resolution of phosphorylated forms on acid urea polyacrylamide gels confirmed that individual variants acquire different levels of phosphorylation during interphase and mitosis, and that these variant-specific differences are conserved between these species [39].

More recently, mass spectrometry (MS) has been used to precisely identify phosphorylation sites in H1 prepared from human, mouse and rat cells [32,33,40–43]. Here we focus on the reports that have utilized chromatographic approaches to resolve individual H1 variants according to phosphorylation levels prior to analysis since they provide information on the relative abundance and site-specificity of differentially modified forms (i.e. mono-, di- and triphosphorylated) during interphase and mitosis. The Lindner group used RP-HPLC to resolve H1.5 from other H1 variants (primarily H1.2, H1.3 and H1.4) expressed in asynchronous CCRF-CEM lymphoblastic T-cells followed by hydrophilic interaction chromatography (HILIC) to resolve individual phosphorylated forms of H1.5 prior to bottom-up MS analysis [41]. HILIC resolved major and minor fractions of monophosphorylated H1.5 corresponding to phosphorylation at S18 and S173, respectively, whereas single fractions were resolved for di- and triphosphorylated H1.5. Their data suggests that H1.5 is phosphorylated hierarchically in an N-terminal to C-terminal fashion during interphase in CCRF-CEM cells, with sequential phosphorylation at S18 > S173 > S189 predominating over S173 > S18 > S189 [41]. This may be a general feature of how H1.5 phosphorylation is regulated as their data suggests that the same is true in human Raji and U937 cells, and in mouse F4N erythroleukemic cells. Analysis of the single RP-HPLC fraction containing H1.2, H1.3 and H1.4 from CCRF-CEM cells identified H1.2-S173, H1.3-S189, H1.4-S172 and H1.4-S187 as major sites of interphase phosphorylation [41]. This same work also identified specific differences in phosphorylation between asynchronously growing cultures (predominantly G1 cells) and colchicine-treated cultures enriched in mitotic cells. H1.5 phosphorylation during interphase localized exclusively to S18, S173 and S189, three sites conforming to the SPXZ cdk substrate consensus motif. These same three sites were phosphorylated in H1.5 from mitotic samples, in conjunction with additional phosphorylation at T11, a non-cdk type site, and at T138 and T155, two TPXZ cdk type sites. Analyses of pentaphosphorylated H1.5 from mitotic samples revealed two phosphorylation isomers in which T11 + S18 + T138 + S173 + S189 or T11 + S18 + T155 + S173 + S189 were phosphorylated, suggesting that phosphorylation at H1.5-T138 and H1.5-T155 may be mutually exclusive [41]. Immunoblotting and immunofluorescence microscopy analyses in HeLa and HEK293 cells with site-specific phosphorylation-

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