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Interplay between histone H1 structure and function

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ABSTRACT

H1 linker histones are involved both in the maintenance of higher-order chromatin structure and in gene regulation. Histone H1 exists in multiple isoforms, is evolutionarily variable and undergoes a large variety of post-translational modifications. We review recent progress in the understanding of the folding and structure of histone H1 domains with an emphasis on the interactions with DNA. The importance of intrinsic disorder and hydrophobic interactions in the folding and function of the carboxy-terminal domain (CTD) is discussed. The induction of a molten globule-state in the CTD by macromolecular crowding is also considered. The effects of phosphorylation by cyclin-dependent kinases on the structure of the CTD, as well as on chromatin condensation and oligomerization, are described. We also address the extranuclear functions of histone H1, including the interaction with the β-amyloid peptide.

1. Introduction

H1 linker histones bind to linker DNA regions on the surface of the nucleosome, protecting the DNA from digestion by micrococcal nuclease. H1 is present at about one molecule per nucleosome in metazoans. H1 is thought to be primarily responsible for the condensation of the thick chromatin fiber. It is currently accepted that histone H1 could have a regulatory role in transcription through the modulation of chromatin higher-order structure. H1 has been considered as a general transcriptional repressor because it contributes to chromatin condensation, which limits the access of the transcriptional machinery to DNA. However, H1 may mediate transcription at a more specific level, participating in complexes that either activate or repress specific genes [1,2]. The exact mechanisms by which H1 is involved in these processes are still obscure.

Protease digestion and NMR analysis showed that under physiological conditions linker histones contain three distinct domains: a short amino-terminal domain (NTD) (20–35 amino acids), a central globular domain (GD) (~80 amino acids), and a long carboxy-terminal domain (CTD) (~100 amino acids) [3]. The terminal domains are highly basic and have little structure in aqueous solution. However, they become fully structured upon interaction with DNA. The secondary structure elements present in the complexes with DNA include α-helix, β-structure, turns and open loops. The terminal domains thus behave as intrinsically disordered proteins with coupled binding and folding [4–6]. Crystallographic and NMR analyses of the GD of chicken erythrocyte H1 and H5 have shown that it contains a winged helix motif [7,8].

H1 has multiple isoforms. In mammals, seven somatic subtypes (designated H1.0–H1.5 and H1.10), a three male germ-line-specific subtype (H1.6, H1.7 and H1.9) and an oocyte-specific subtype (H1.8) have been identified [9]. H1 subtypes have different affinities for DNA and chromatin and affect the nucleosome repeat length (NRL) [10–14]. The binding properties of the histone H1 subtypes are mainly determined by the CTD. Fluorescence Recovery After Photobleaching (FRAP) and in vitro competitive assays led to the classification of H1 subtypes into three major binding groups. [10,15]. The kinetics of H1 subtype exchange is further modulated by post-translational modifications (PTMs) and by interactions with other proteins. Breast cancer cells depleted of individual histone H1 subtypes, displayed specific phenotypes. These observations support the view that distinct roles exist for the linker histone subtypes [16]. These studies also revealed a correlation between binding affinity and the length of the CTD in the different H1 subtypes.

The classical tripartite structure of H1 histones is found in higher eukaryotes. Some protists such as *Tetrahymena thermophila*, have proteins that are similar to the C-terminal domain [17]. On the other hand, yeast has an H1-like nuclear protein with the classical three-domain structure plus an extra globular domain [18].

H1-like proteins can be traced back to eubacteria, but the GD was acquired later in evolution. The most conserved region of histone H1 is the globular domain. The N- and C-terminal domains are, in general, more variable. The H1 subtypes show a wide variety of substitution rates, which is in favor of their functional differentiation [19].

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H1 histones are targets of several post-translational modifications, including phosphorylation, acetylation, methylation, formylation, ubiquitination, deamidation and citrullination. Some H1 modifications, like the methylation of K26 of H1.4, have been associated with the binding of protein factors [20]. There is also increasing evidence of the role of epigenetic H1 modifications in cancer [20]. Further data about new PTMs are thus necessary in order to characterize their role in transcriptional regulation and disease.

The main post-translational modification affecting histone H1 is phosphorylation of the consensus sequences, (S/T)-P-X-(K/R), by cyclin-dependent kinases (CDKs). In mammalian subtypes, these sequences are located mostly in the CTD. During interphase, H1 subtypes are present as a mixture of unphosphorylated and low-phosphorylated forms, according to the particular subtype and cell line and the moment of the cell cycle [21]. Phosphorylation decreases the residence time of H1 in chromatin [15,22]. It has also been shown that phosphorylation of the CTD by CDK greatly affects its DNA-bound structure and DNA aggregation capacity [23]. Partial phosphorylation drastically reduced DNA aggregation, but full phosphorylation restored to a large extent the aggregation capacity of the unphosphorylated domain. Similar results were obtained with chromatin partially phosphorylated, regarding condensation, oligomerization and associated structural effects [24]. These results suggest the involvement of H1 hyperphosphorylation in metaphase chromatin condensation and of partial phosphorylation in interphase chromatin relaxation.

Although the primary role of histone H1 is binding to DNA in cell nuclei, H1, and in particular the H1.2 subtype, can also be found in the cytoplasm and on cellular membranes of neurons and astrocytes in prion diseases and Alzheimer's disease (AD) [25]. Histone H1 is also involved in cellular processes including apoptosis, neutrophil extracellular trap (NET) formation and T-cell response. Additionally, H1 and its terminal domains have antimicrobial properties [26,27].

In this review we focus on the interplay between structure and function of histone H1, particularly in its terminal domains. We also discuss some of the extranuclear functions of histone H1, in particular the interaction with the β-amyloid peptide in Alzheimer disease.

2. N-terminal domain

The N-terminal domain (NTD) of histone H1 is the shortest domain of the protein with a length of between 20 and 35 residues, depending on the subtype. The N-terminus can be divided into two sub-regions [28]. The distal part of the NTD is enriched in hydrophobic residues, whereas a highly basic region is found close to the globular domain [28]. The NTD is considered to be mainly unstructured in solution, but NMR studies of peptides derived from the NTD of the subtypes H1.0 and H1.4 (equivalent to H1e) show that the basic cluster can adopt α-helical structure in the presence of trifluoroethanol (TFE), which is a stabilizer of secondary structure [5,29]. The NTD of H1.4 contains two α-helical regions; the first includes the residues from T17 to A27, and the second the residues from G29 to T34 (this numbering does not include the initial methionine). The helical elements are connected by a Gly–Gly motif. Structure calculations show that the Gly–Gly motif behaves as a flexible linker between the helical regions. The wide range of relative orientations of the helical axes allowed by the Gly–Gly motif may facilitate the tracking of the phosphate backbone by the helical elements or the simultaneous binding of two nonconsecutive DNA segments in chromatin (Fig. 1A) [29].

The study of two peptides belonging to the NTD of H1.0 revealed the presence of a single α-helical element, spanning from K11 to D23, with the first three basic residues, K11, K13 and R14, on one side of the helix and the following three basic residues, K16, K19 and K20, on the other side (Fig. 1B). The analysis of the complexes of these peptides with DNA by Fourier Transform Infrared Spectroscopy (FTIR) showed the induction of α-helix with percentages in agreement with the helical propensities observed in TFE. This result indicates that the basic region of the NTD is an intrinsically disordered region with coupled binding and folding [5].

The NTD has been shown to be non-essential for the formation of higher-order chromatin structures, but its deletion appears to reduce the affinity of H1 for chromatin [30]. FRAP analysis of chimeric H1, where the NTD of H1.0 and H1.2 had been swapped, suggests that the NTD contributes to the differential binding affinities of the subtypes [31]. The induction of α-helix within the NTD could be essential for its proper binding to chromatin.

Post-translational modifications could also play a role in the structure and function of the NTD. Although the NTD is the most variable region in histone H1 [19], several modified positions are conserved in avian and mammalian somatic subtypes, including S1, T3, K17 and K34, which suggests a specific role in H1 function [32]. Of particular interest is K34, which is mainly acetylated, but it is also found methylated in mouse. Genome-wide analysis has shown that human H1.4 acetylated at K34 is enriched at transcription start sites (TSS) and correlates with high H3K4me3 occupancy, a mark of active chromatin. The presence of the H1.4K34ac in TSS increases H1 mobility and thus stimulates transcription. Furthermore, the modified protein can recruit TAF1, a subunit of the TFIID transcription factor [33].

The presence of K26 in H1.4 is necessary for cell proliferation and heterochromatin loading [34]. Adjacent modifications in K26 and S27 of the NTD of H1.4 have been thoroughly studied [20,35,36]. Methylation at K26 is involved in the binding of histone H1 to heterochromatin protein 1 (HP1), and it is thought to act in synergy with H3K9me3 [20]. Both methylated positions, H1.4 K26 and H3K9, are located within an ARKS/T motif, which is recognized by the HP1-like chromodomains [37].

Phosphorylation of S27 disrupts the interaction between H1 and HP1, which suggests that this interaction is regulated by a methyl-phos switch [35]. Hergeth et al. have shown that S27 is specifically phosphorylated by Aurora kinase during mitosis. Moreover, phosphorylation at this position appears to be favored by dimethylation or trimethylation of K26, suggesting that this could be a mechanism for dissociating HP1 from mitotic chromatin [36]. FRAP experiments have shown that this modification slows down the fluorescence recovery, suggesting a stronger binding of H1 to chromatin during mitosis.

Other H1 residues belonging to the NTD are phosphorylated in mitosis. Positions S1 and T3 have been found phosphorylated in most subtypes [32]. An additional site of phosphorylation has been described at T10 of H1.5 in CEM cells [38]. These phosphorylation sites are not CDK consensus sequences and the kinases involved have not been identified. Additional studies are needed in order to uncover the structural and functional impact of PTMs on the NTD.

3. Globular domain

The central globular domain of histone H1 (GD) has about 80 amino acids and is highly conserved among different species [19]. The GD is necessary for generating the 168 bp chromatosome particles observed during micrococcal nuclease digestion of native chromatin, and is sufficient for specific binding to the nucleosome in vitro [39].

The structure of the globular domain of chicken H5 has been determined by single-crystal X-ray crystallography [7], while the structure of the GD of avian H1 and yeast H1 has been determined in solution by nuclear magnetic resonance [8,18]. Comparison of the three structures revealed a remarkable similarity in the 3D structure of the GD [18,40].

The GD contains a helix-turn-helix (HTH) motif, also known as winged-helix fold. The HTH motif, a DNA-binding motif, consists of three α-helices with a C-terminal β-hairpin. An antiparallel β-sheet is formed between the C-terminal β-hairpin and a short β-strand connecting the first and second α-helices. The HTH motif has been found in other proteins, such as the CAP transcription factor (catabolite gene-activator protein) and HNF3γ (hepatocyte nuclear factor-3γ) [7].

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