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Review

Quickly evolving histones, nucleosome stability and chromatin folding: All about histone H2A.Bbd

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Abstract

Histone H2A.Bbd (*B*arr *b*ody-*d*eficient) is a novel histone variant which is largely excluded from the inactive X chromosome of mammals. Discovered only 6 years ago, H2A.Bbd displays very unusual structural and functional properties, for instance, it is relatively shorter and only 48% identical compared to H2A, lacking both the typical C-terminal tail of the H2A family and the very last sequence of the docking domain, making it the most specialized among all histone variants known to date. Indeed, molecular evolutionary analyses have shown that H2A.Bbd is a highly hypervariable and quickly evolving protein exclusive to mammalian lineages, in striking contrast to all other histones. Different studies have described a deposition pattern of H2A.Bbd in the chromatin that overlaps with regions of histone H4 acetylation suggesting its association with transcriptionally active euchromatic regions of the genome. In this regard, it is believed that this histone variant plays an important role in determining such regions by destabilizing the nucleosome and locally unfolding the chromatin fiber. This review provides a concise, comprehensive and timely summary of the work published on H2A.Bbd structure and function. Special emphasis is placed on its chromatin deposition patterns in relation to gene expression profiles and its evolutionary history, as well as on the dynamics of H2A.Bbd-containing nucleosomes.

Keywords: Chromosomes; Histone variants; Nucleosomes; Gene expression; Evolution

1. Introduction

In eukaryotes, DNA is found associated with histones forming the chromatin, a nucleoprotein complex that allows packaging of the genomic DNA within the nucleus and also provides the support for most DNA metabolic functions. The repetitive subunit of chromatin, the nucleosome, consists of an octamer of core histones (two each of H2A, H2B, H3 and H4) around which two left handed superhelical turns of DNA are wrapped (van Holde, 1988). The *n*ucleosome *c*ore *p*articles (NCPs) are linked together in the chromatin fiber by short stretches of linker DNA that with the collaboration of linker H1 histones which bind to these regions, results in an additional folding of the chromatin fiber.

The nucleosome represents a barrier to the accessibility of transcription factors to DNA and interferes with several vital cellular processes. The cell uses different strategies to overcome this nucleosome barrier, including histone *p*ost-*t*ranslational *m*odifications (PTMs) (Strahl and Allis, 2000), chromatin remodeling complexes (Lusser and Kadonaga, 2003), and the incorporation of specific histone variants within the histone octamer (Henikoff and Ahmad, 2005). This latter mechanism is the least understood. Histone variants are used by the cell to

Abbreviations: Bbd, Barr body-deficient; BER, Base Excision Repair; EMSA, Electrophoretic Mobility Shift Assay; FRAP, Fluorescence Recovery After Photobleaching; FRET, Fluorescence Resonance Energy Transfer; NAP, Nucleosome Assembly Protein; NCP, Nucleosome Core Particle; PTM, Post-Translational Modification.

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build specialized nucleosomes by replacing canonical histones at different stages of the cell cycle and generating an architecturally and functionally distinct chromatin structure (Ausió and Abbott, 2002). The histone H2A family encompasses the greatest diversity of variants among core histones which can substitute canonical replication-dependent H2A (Redon et al., 2002; Malik and Henikoff, 2003; Sarma and Reinberg, 2005). Such diversity could reflect both the more labile interaction of the H2A–H2B dimer with the remaining histones and DNA (van Holde, 1988) and its strategic position (being the main contributor of acidic residues to the 'acidic patch') within the core particle (Luger et al., 1997).

2. Histone H2A.Bbd and H2A.Bbd-nucleosomes

Histone H2A.Bbd (*B*arr *b*ody-*d*eficient), which is the newest described H2A variant until now, was first characterized in humans (Chadwick and Willard, 2001) and shown to be excluded from the female inactive X chromosome from whence its name was derived. Its distribution overlaps with regions of histone H4 acetylation in the nucleus suggesting its association with transcriptionally active euchromatic regions of the genome (Chadwick and Willard, 2001).

2.1. Histone H2A.Bbd structure

The H2A.Bbd protein consists of 115 amino acids, with a molecular weight of 12.7 kDa (Fig. 1). It is the most distantly related variant to canonical histone H2A sharing only 48% sequence identity, and making it the most specialized among all histone variants known to date. The histone fold encompasses the region of highest amino acid conservation, probably due to its critical role for the correct positioning of H2A.Bbd within the nucleosome and for its interactions with the DNA double helix. This variant is also considerably shorter than other histones of the H2A family of proteins and its N-terminal tail exhibits a row of six arginines and a conspicuous absence of lysines, which could be important for its function (Bao et al., 2004; Gautier et al., 2004). The lack of an extensive C-terminal tail (typical of the H2A family) as well as of the very last sequence of the docking domain responsible for interactions with H3 in major NCPs is also a characteristic feature of H2A.Bbd (Chadwick and Willard, 2001; Bao et al., 2004). Additionally, it lacks the residues that contribute to the NCP "acidic patch" (Luger et al., 1997) and it contains only one lysine residue in its entire amino acid sequence compared to fourteen in canonical H2A, and this results in a slightly less basic protein. Consequently, the residues amenable for PTMs in canonical H2A molecules including acetylation, phosphorylation and ubiquitination (Luger and Richmond, 1998) are not conserved in H2A.Bbd, suggesting that this histone variant could be regulated in a different fashion compared to other members of the H2A family.

2.2. Recruitment of H2A.Bbd to nucleosomes and chromatin stability

The very unusual structural and functional properties displayed by H2A.Bbd result in modification of the nucleosomal structure by altering its stability, modifying its interaction with transcription factors, and affecting its mobilization by different remodeling complexes (Angelov et al., 2004; Bao et al., 2004; Gautier et al., 2004; Okuwaki et al., 2005; Angelov

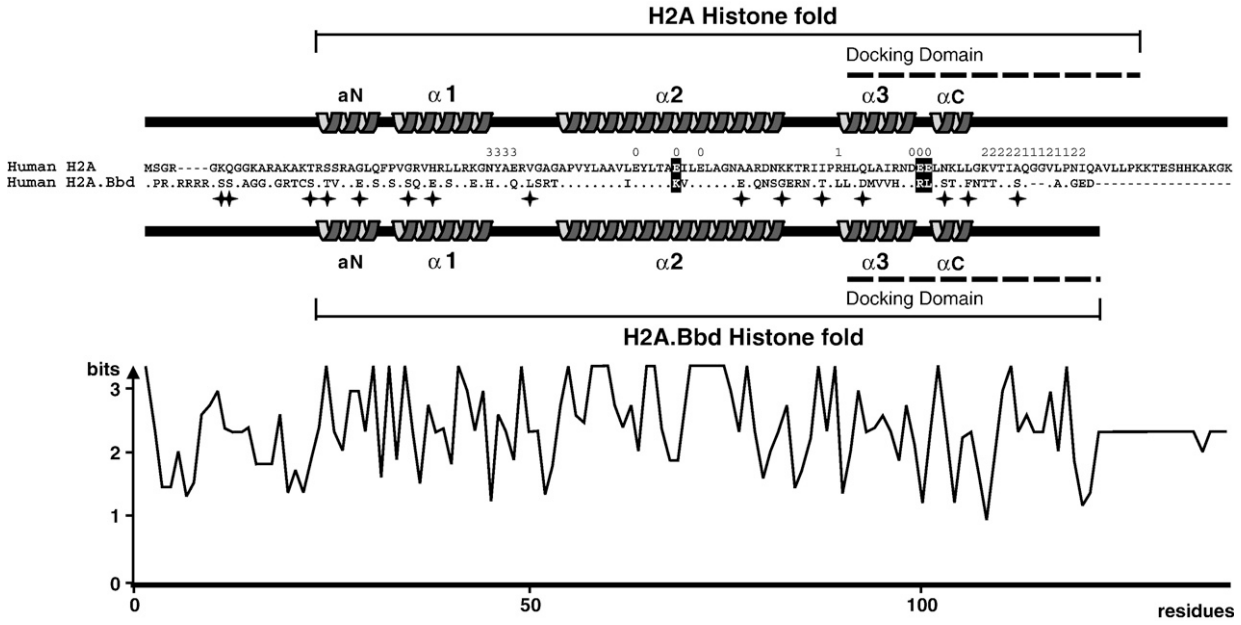

Fig. 1. Amino acid alignment of the human canonical H2A and the H2A.Bbd histone variants, indicating the region corresponding to the histone fold domain and the docking domain in each case. The residues of H2A that are part of the nucleosome acidic patch are indicated in white and in black boxes, black stars below the alignment denote positions with fixed amino acid changes in the H2A.Bbd variant respect to the canonical H2A among mammals. Numbers 0, 1, 2, and 3 above the alignment indicate specific residues involved in internucleosomal contacts, H2A/H3 contacts, H2A/H4 contacts, and H2A/H2A contacts, respectively. The graphic represents the amino acid variability in comparisons across H2A/H2A.Bbd proteins from mammals. In this representation, the height of the peaks is proportional to the conservation of the corresponding amino acid site (Eirín-López et al., 2008).

et al., 2006; Doyen et al., 2006; Menoni et al., 2007). Histone H2A.Bbd has been shown to cofractionate and copurify with core histones in the nucleosome after chromatin fractionation and sedimentation (Chadwick and Willard, 2001). In combination with *e*lectrophoretic *m*obility *s*hift *a*ssay (EMSA) experiments, these observations revealed that H2A.Bbd is efficiently incorporated into nucleosomes (Angelov et al., 2004; Gautier et al., 2004) by replacing canonical H2A molecules within the NCP. However, H2A.Bbd nucleosomes exhibit numerous structural perturbations compared to conventional nucleosomes, unveiling a weaker thermodynamic stability in the H2A.Bbd nucleosome. Indeed, these perturbations include alterations in the DNase I footprinting pattern that were observed all along the H2A.Bbd nucleosomal DNA (Angelov et al., 2004).

Although ectopically expressed H2A.Bbd colocalizes with the other three core histones *in vivo*, *in vitro* analyses of H2A.Bbd-containing complexes demonstrated that this variant does not form a stable histone octamer in the absence of DNA. These results suggest the presence of a destabilized interface between the H2A.Bbd–H2B dimer and the $(H3–H4)_2$ tetramer (Bao et al., 2004; Eirín-López et al., 2008).

Analytical ultracentrifugation experiments have shown that the H2A.Bbd-NCP has a more elongated shape than the canonical NCP (Gautier et al., 2004), which may be the reason for the slow electrophoretic mobility observed of H2A.Bbd-NCP's (Bao et al., 2004). The behavior exhibited by H2A.Bbd-nucleosomes as a result of variations in the ionic environment was also studied by analytical centrifugation. These studies revealed that H2A.Bbd is less tightly bound compared to canonical H2A in the NCP, suggesting a lower inherent stability of the H2A.Bbd particle (Gautier et al., 2004; Eirín-López et al., 2008).

In spite of the fact that previous experiments suggested that H2A.Bbd-nucleosomes exhibit lower stability compared to canonical nucleosomes, direct measurements of the forces maintaining the structure of the H2A.Bbd particle showed that the magnitude of the force necessary to unfold a single H2A.Bbd-NCP is very similar to that required to unfold a canonical nucleosome (Doyen et al., 2006). In addition, *f*luorescence *r*ecovery *a*fter *p*hotobleaching (FRAP) experiments demonstrated that H2A.Bbd exchanges from chromatin much more rapidly than canonical H2A within the nucleosome *in vivo* (Gautier et al., 2004). This observation was later confirmed using the histone chaperone *n*ucleosome *a*ssembly *p*rotein I (NAP-I) (Okuwaki et al., 2005), which efficiently provokes the assembly and disassembly of the H2A.Bbd–H2B dimers from the NCPs. Therefore, all the available data is compatible with a lower stability of the variant H2A.Bbd-nucleosome compared with canonical nucleosomes and with this histone variant being closely associated with acetylated euchromatic regions of the genome and possibly with active genes (Chadwick and Willard, 2001).

3. H2A.Bbd and the folding of the chromatin fiber

3.1. Role of the docking and acidic patch domains

Bao et al. (Bao et al., 2004) found that H2A.Bbd-NCP had a more relaxed structure in which a segment of only 118±2 bp of DNA is protected against digestion with micrococcal nuclease. However, micrococcal nuclease digestion experiments in combination with microscopy techniques (atomic force microscopy and electron cryo-microscopy) concluded that the H2A.Bbd-nucleosome organizes 130 bp of DNA in contrast to the 147 bp tightly organized in canonical NCPs). This suggests that 10 bp at each end of the nucleosomal DNA are released from the octamer (Doyen et al., 2006). In addition, the electron micrographs clearly showed that canonical and H2A.Bbd-NCPs exhibit different conformations. While the majority of the entry and exit DNA ends of conventional nucleosomes formed a V-type structure with the NCP located at a middle position, only a small fraction of H2A.Bbd particles exhibited such a structure. Indeed, H2A.Bbd-nucleosomal DNA ends formed an angle close to 180° in most cases. This observation suggests that the H2A.Bbd octamer interacts weakly with the entry/exit nucleosomal DNA and it is unable to generate a stable V-type orientation of the free DNA ends (Fig. 2A).

Histone H2A.Bbd lacks the C-terminus characteristic of the H2A family as well as the very end of the docking domain shown to be involved in the interaction with H3 in the nucleosome (Chadwick and Willard, 2001; Bao et al., 2004). The absence of *f*luorescence *r*esonance *e*nergy *t*ransfer (FRET) between the ends of the DNA in H2A.Bbd-NCPs indicates that the distance between the DNA ends increases significantly, suggesting that these are less constrained in H2A.Bbd-NCPs and partially dissociated from the surface of the histone octamer, resulting in a less compact structure (Fig. 2A). In order to investigate which regions of H2A.Bbd are responsible for this behavior, chimeras of H2A in which domains between H2A.Bbd and canonical H2A have been swapped were analyzed. These experiments demonstrated that the H2A.Bbd docking domain is largely responsible for the altered conformation and the looser DNA organization observed in H2A.Bbd-NCPs. Thus, the H2A.Bbd-docking domain and not the missing C-terminal tail appears to be the principal region responsible for either directly or indirectly organizing the 10 penultimate base pairs of nucleosomal DNA in H2A.Bbd-NCPs (Fig. 2B) (Bao et al., 2004).

To test whether the divergent docking domain of H2A.Bbd is involved in the generation of the specific properties of the H2A.Bbd-nucleosome, Doyen et al. (Doyen et al., 2006) produced an H2A.Bbd mutant in which the docking domain was substituted for the docking domain and the C-terminal tail of a canonical histone H2A. Results showed that this mutant was able to generate a NCP with some of the characteristic properties of the canonical H2A-NCP. For instance, the length of the DNA organized by the histone octamer and the *in vitro* stability of the nucleosomal particle containing the fusion protein were very similar to what was obtained with the particle containing the canonical H2A protein. In contrast, the incorporation of the fusion protein in nucleosomal particles led to an assembly of only a subset of particles with the V-type conformation characteristic for the conventional nucleosomes and to only a partial rescue of the efficiency of nucleosome mobilization by SWI/SNF (Doyen et al., 2006). These results support the notion that the stability and the nucleosomal DNA organization in H2A.Bbd-nucleosomes are in part dependent on the docking

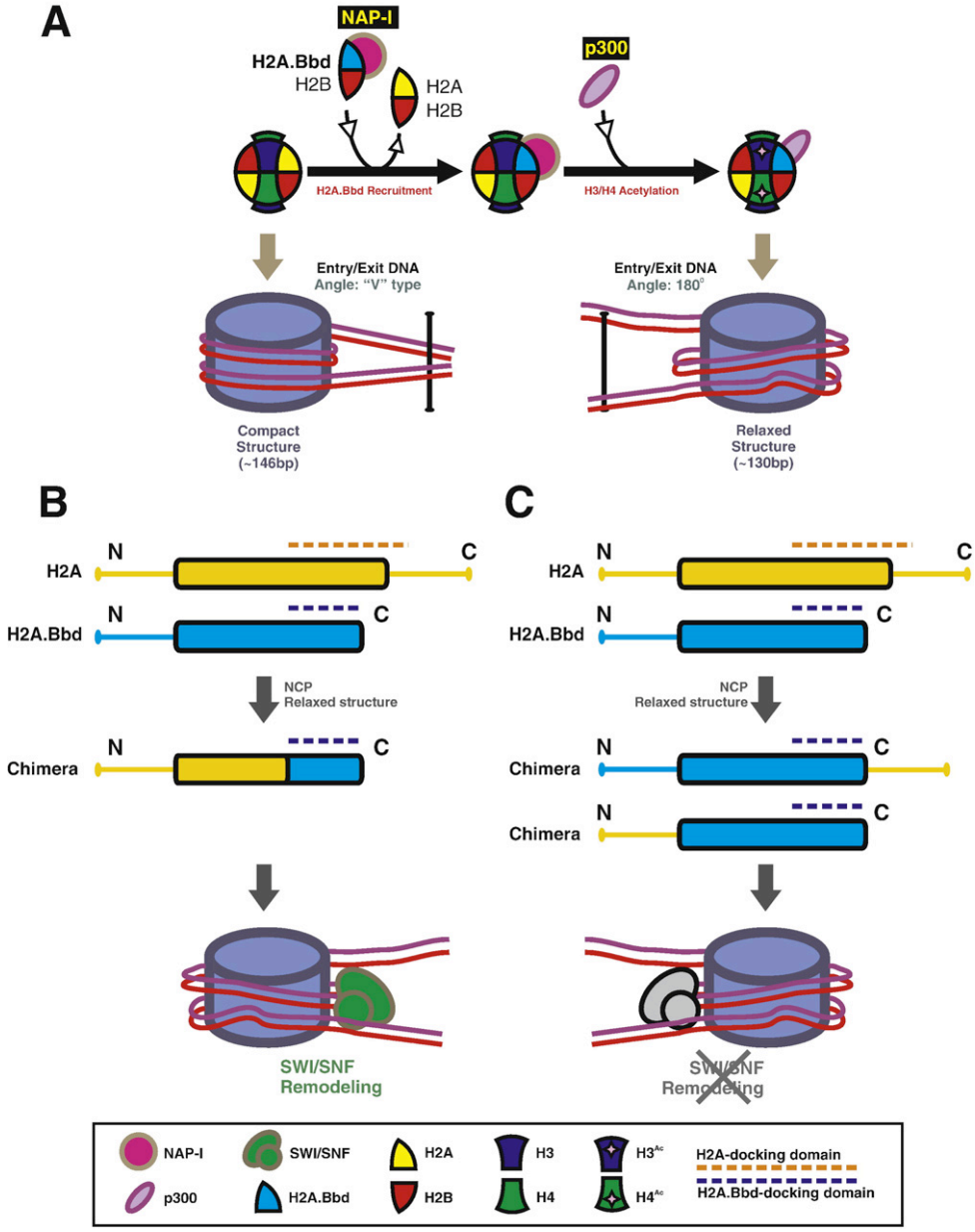

Fig. 2. (A) H2A.Bbd–H2B dimers are incorporated into the nucleosome by the NAP-I binding protein. This protein mediates the assembly and disassembly of the H2A.Bbd–H2B dimers from NCPs more effectively than dimers containing H2A histone variants (Okuwaki et al., 2005), conferring the NCP with a more flexible structure. The incorporation of H2A.Bbd into the nucleosome increases the efficiency in the acetylation of the histone tails by p300, at the N-terminal tails of H3 and H4 directly associated with transcriptional activation (An et al., 2002). (B) Domain swapping experiments indicate that the docking domain from H2A.Bbd (and not the missing C-terminal tail) is largely responsible for the altered conformation and the looser DNA organization observed in H2A.Bbd-NCPs. (C) Presence of the histone fold domain of H2A.Bbd in a nucleosomal particle (but not its peculiar N-terminus or the absence of the C-terminal tail) is sufficient to generate structural properties that prevent the remodeling by SWI/SNF.

domain of H2A.Bbd. However, the whole histone fold domain of H2A.Bbd is otherwise responsible for the weaker mobilization of the H2A.Bbd-nucleosome by SWI/SNF (see below), among other structural and functional properties (Fig. 2B–C). Furthermore, a recent report has shown that the alteration of the acidic patch in H2A.Bbd-containing nucleosomes impairs the magnesium-dependent internucleosomal interactions that lead to the folding of nucleosome arrays (Zhou et al., 2007). Thus, it seems that alterations of both the docking and acidic patch domains can in differentand non-exclusive ways, contribute to maintaining the chromatin fiber in an unfolded state.

3.2. ATP-dependent remodeling of H2A.Bbd-nucleosomes

The H2A.Bbd-nucleosome exhibits distinct structural and functional properties, including an inability to be mobilized by the remodelers SWI/SNF and the ACF machineries, although the binding of these remodeler complexes to chromatin is not affected by the presence of the histone H2A.Bbd in the nucleosomes (Angelov et al., 2004). Experiments with reconstituted nucleosomes consisting of swapped-tail mutants were used in order to analyze the mechanism and the role of different H2A.Bbd domains in the interference of the SWI/SNF-

mediated remodeling process (Doyen et al., 2006). It was found that SWI/SNF was unable to remodel nucleosome particles reconstituted with swapped tail H2A–H2A.Bbd mutants containing the H2A.Bbd histone fold domain (Fig. 2C). Therefore, it seems that the presence of the histone fold domain of H2A.Bbd in a nucleosomal particle but not its peculiar N-terminus or the absence of the C-terminal tail is sufficient to generate structural properties that prevent the remodeling by SWI/SNF. In addition, the presence of the histone chaperone nucleolin, which is able to increase the efficiency of the chromatin remodelers SWI/SNF in nucleosomes containing the variant macroH2A, is not able to induce the remodeling of H2A.Bbd-nucleosomes by SWI/SNF (Angelov et al., 2006). Furthermore, it was shown that SWI/SNF stimulates *b*ase *e*xcision *r*epair (BER) of conventional nucleosomes, but not of H2A.Bbd-nucleosomes (Menoni et al., 2007).

4. H2A.Bbd and gene expression

Although H2A.Bbd is presumably distributed almost throughout the nucleus, it now seems clear that its exclusion from the inactive X chromosome has critical implications for the regulation of gene expression. It has been suggested that the presence of H2A.Bbd within the NCP may alter the conformation of the nucleosome in an acetylation-independent way (Eirín-López et al., 2008), increasing the accessibility of protein complexes involved in activation of transcription to the DNA. In this regard, the association of H2A.Bbd with transcriptionally active regions suggests that this histone variant facilitates gene expression through the relaxation of chromatin structure, a notion that is further supported by its exclusion from the heterochromatic inactive X chromosome and by its association with the very few regions that escape inactivation on this chromosome (Chadwick and Willard, 2001). In contrast to the inability of H2A.Bbd-nucleosomes to be mobilized by remodeling complexes, the p300-activated transcription appeared to be more efficient for H2A.Bbd-nucleosomal arrays than for canonical H2A arrays. Indeed, the incorporation of H2A.Bbd into nucleosomes leads to better efficiency in the acetylation of the histone tails by p300, which may result in an increase in transcriptional activation (Fig. 2A) (Angelov et al., 2004). Although the association of H2A.Bbd with transcriptionally active regions seems to be the most widespread notion, the reconstitution of H2A.Bbd-containing nucleosomal arrays also unveiled their ability to significantly repress basal transcription, which could be alleviated by transcriptional activators like Tax and CREB (Bao et al., 2004).

Besides the marked deficiency of H2A.Bbd in the inactive X chromosome, its presence is mutually exclusive with macroH2A, another H2A variant that is otherwise enriched on the inactive X

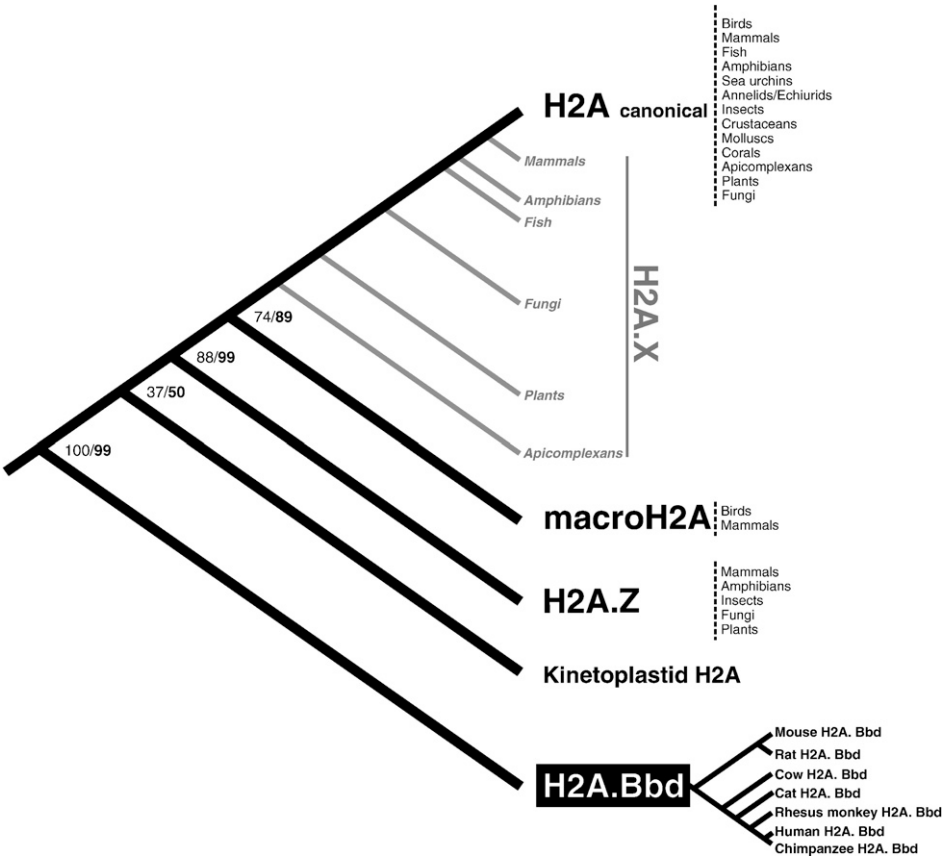

Fig. 3. Phylogenetic relationships among H2A proteins as previously described by (Eirín-López et al., 2008). All H2A lineages have a monophyletic origin with the exception of H2A.X, which shows a recurrent evolutionary origin across eukaryotes. The H2A.Bbd lineage represents the variant with highest levels of divergence, which is characterized by its apparent early origin in H2A evolution. Numbers at the nodes indicate the confidence values (bootstrap and interior branch test) for the groups of sequences defined by the tree.

chromosome (Pehrson and Fried, 1992; Costanzi and Pehrson, 1998). In contrast to H2A.Bbd, whose presence could be viewed as a marker of active chromatin, macroH2A is a highly dynamic chromatin silencer (Ausió, 2006) that stabilizes the NCP (Abbott et al., 2005) and interferes with SWI/SNF nucleosome remodeling (Angelov et al., 2003). Further high-resolution analyses will be necessary in order to demonstrate if both histone variants represent functional antagonists in which each counterpart would be implicated in different ways of regulating gene expression, silencing in the case of macroH2A and activating in the case of H2A.Bbd.

5. Evolutionary history of the H2A.Bbd lineage

Molecular evolutionary analyses have revealed that histone H2A.Bbd is a quickly evolving hypervariable mammalian histone variant, in striking contrast to all other histones known to date (Malik and Henikoff, 2003; Eirín-López et al., 2008). Histone H2A.Bbd presents a high extent of variation with respect to canonical H2As with a trend towards the loss of basic residues. Also, as mentioned earlier, the acidic residues of H2A which contribute to the nucleosome 'acidic patch' (E69, E100, and E101) (Luger et al., 1997) are replaced by basic and non-polar residues in the case of H2A.Bbd (Fig. 1). In addition to the absence of the 'acidic patch' that is involved in inter-nucleosomal interactions, H2A.Bbd also has alterations in sites involved in intranucleosomal histone-histone interactions (Eirín-López et al., 2008). From a phylogenetic point of view the H2A.Bbd lineage encompasses the highest levels of divergence with respect to the remaining H2A lineages and, although it has only been identified in mammals, it appears that H2A.Bbd represents a quickly evolving variant with a primitive origin early in H2A evolution (Fig. 3) (Eirín-López et al., 2008).

The high levels of genetic divergence presented by the protein members of the H2A.Bbd family in mammals have been shown to be the result of the accumulation of nonsynonymous changes, that affect mainly the regions of the molecule outside of the histone fold. Because the unique structural signature of the H2A.Bbd histone fold is very important for its intrinsic role in destabilizing the inter- and intranucleosomal interactions (Zhou et al., 2007) the corresponding region of the gene appears to have been less affected by the nonsynonymous variation. Although H2A.Bbd displays the lowest levels of synonymous nucleotide variation among the different H2A lineages, this is still significantly greater than the nonsynonymous variation. This suggests the presence of a negative or purifying selection acting on this histone variant, as in the case of the remaining H2A variants (Eirín-López et al., 2008).

6. Concluding remarks

Studies carried out during the last 6 years indicate that H2A.Bbd participates in destabilization of nucleosomes and unfolding of the chromatin fiber, possibly facilitating the interaction with different transcription factors, chromatin modifying enzymes and polymerases that facilitate gene expression. In addition, it seems that the presence of this variant increases the efficiency in the acetylation of the histone tails. Since H2A.Bbd-nucleosomes seem to have a more relaxed structure and exhibits an overlapping nuclear distribution with acetylated histone H4, it was proposed that the role of this variant is in the assembly and maintenance of transcriptionally active chromatin. Histone H2A.Bbd is exceptional not only for conferring very unusual structural properties on the nucleosome, but also for lacking the usual targets amenable for post-translational modifications in canonical H2A. The uniqueness of histone H2A.Bbd makes this variant very attractive for further studies related to its role in chromatin dynamics. No matter which kind of results, they will keep surprising us in the most unforeseen way.

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