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MINI-REVIEW

The specificity of H2A.Z occupancy in the yeast genome and its relationship to transcription

Vishwanath R. Iyer[1]

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Abstract

The incorporation of histone variants into nucleosomes has important functional consequences in all aspects of eukaryotic chromatin biology. H2A.Z is a conserved histone variant found in all eukaryotes from yeast to mammals. Recent studies in yeast have shed light on the questions of where and how nucleosomes containing this variant are situated at promoters and in relation to genes, and what its specificity implies with regard to transcription. In yeast, H2A.Z appears to be primarily incorporated into the first nucleosome in the direction of transcription initiation, either of an mRNA transcript or a divergently transcribed upstream antisense non-coding RNA. This specificity of H2A.Z is due in part to the localization at promoters of SWR1, the ATP-dependent chromatin remodeler that incorporates H2A.Z into nucleosomes. Replacement of H2A.Z with canonical H2A is dependent on the function of the transcription pre-initiation complex. The recent studies summarized in this review reveal that the directionality of H2A.Z occupancy in relation to transcription thus reflects a balance of incorporation and eviction activities, which likely have varying contributions at distinct sets of genes across the genome.

Keywords H2A.Z · Histone variant · Nucleosome · SWR1 · INO80

Introduction

The long and linear genomic DNA in eukaryotic chromosomes has to be systematically compacted to fit within the confines of the nucleus. The first level of compaction of the eukaryotic genome occurs by the wrapping of DNA in a left-handed superhelix around a histone octamer to form nucleosomes. Incorporation of histone variants, post-translational modifications of histones, and the positioning of nucleosomes along the DNA influence all processes that the genomic DNA participates in, including transcription, DNA replication, repair, and higher order chromosomal organization. The canonical histones H2A, H2B, H3, and H4 constitute the standard nucleosome octamer, which comprises an H3–H4 tetramer and two H2A–H2B dimers. The incorporation of non-allelic alternative versions of certain histones, or histone variants, is one mechanism by which the uniform nucleosomal structure of chromatin is altered, with important functional consequences. Many histone variants have been identified, but the centromere-specific H3 variants (CenH3) (Ichikawa and Kaufman 2019) and the H2A variant H2A.Z are considered to be universal histone variants given their presence in all domains of eukaryotes. The variant H2A.Z is found in virtually all eukaryotes from yeast and protozoa to plants and metazoans (Talbert and Henikoff 2010). H2A.Z is essential in mouse and other organisms, whereas in yeast, its absence causes condition-specific growth phenotypes (Jackson and Gorovsky 2000; Santisteban et al. 2000; Zlatanova and Thakar 2008). Given its conservation across the many organisms it is found in, and its incorporation into nucleosomes at yeast promoters, it is only natural that many recent insights into H2A.Z function and its relationship to transcription come from studies in yeast. This mini-review focuses on the mechanisms of incorporation of H2A.Z into RNA polymerase II (RNAPII) promoters in the yeast *Saccharomyces cerevisiae* and how H2A.Z occupancy of promoters relates to transcriptional activity.

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✉ Vishwanath R. Iyer
vishy@utexas.edu

[1] Department of Molecular Biosciences, Institute for Cellular and Molecular Biology, Livestrong Cancer Institutes, Dell Medical School, University of Texas, Austin, TX 78712, USA

The H2A.Z histone variant in *Saccharomyces cerevisiae*

In yeast, H2A.Z is about 56% identical to canonical H2A at the protein level (Fig. 1a), whereas it is 65% identical to human H2A.Z. The overall structure of the nucleosome containing H2A.Z is similar to the canonical nucleosome (Fig. 1b), though the amino acid changes in the variant are thought to slightly destabilize interactions between the H2A.Z–H2B dimer and the H3–H4 tetramer (Suto et al. 2000). H2A.Z has been reported to have roles in transcription, DNA replication and repair, chromosome condensation, heterochromatin formation and silencing, and mitosis (Giaimo et al. 2019; Long et al. 2020; Yamada et al. 2018; Zlatanova and Thakar 2008). Interestingly, the incorporation of H2A.Z has been reported to both stabilize as well as destabilize the resulting nucleosome, particularly with regard to how it affects transcription (Weber et al. 2014; Zlatanova and Thakar 2008). Deletion of the *HTZ1* gene in yeast, which encodes H2A.Z, does not lead to strong transcriptional effects. The relationship of H2A.Z with overall transcriptional activity of a gene could be either positive or negative, given that it has been reported to be associated with actively transcribed genes as well as repressed genes.

The locations of canonical nucleosomes as well as nucleosomes containing histone variants throughout the genome have been mapped at high resolution using methods that combine micrococcal nuclease (MNase) digestion of linker DNA between nucleosomes, chromatin immunoprecipitation (ChIP) and the use of high-resolution microarrays or deep sequencing. In yeast, H2A.Z-containing nucleosomes are found at the promoter, which typically contains a nucleosome-depleted region (NDR) where the transcription pre-initiation complex (PIC) can assemble (Yague-Sanz et al. 2017). The first nucleosome in the direction of transcription downstream of the NDR is typically referred to as the + 1 nucleosome, which contains the transcription start site (TSS), while the first nucleosome in the upstream direction is labeled the − 1 nucleosome (Fig. 1c). The TSS is generally 50–60 bases upstream of the + 1 nucleosome dyad (the midpoint), meaning that the RNA is initiated about 10 bp inside the + 1 nucleosome (Lee et al. 2007; Yuan et al. 2005). Genome-wide maps of H2A.Z localization in yeast showed that it occupies promoters and is incorporated into the flanking + 1 and − 1 nucleosomes (Albert et al. 2007; Guillemette et al. 2005; Li et al. 2005; Raisner et al. 2005; Zhang et al. 2005).

The role of SWR1 in H2A.Z incorporation

What is the mechanism of the remarkable specificity of H2A.Z incorporation at promoters in the yeast genome? To a considerable extent, it is dictated by the localized action of the SWR1 complex, the chromatin remodeler responsible for incorporating H2A.Z into the nucleosome. SWR1 belongs to the ATP-dependent chromatin remodeler family that includes SWI/SNF and other ATPases (Kobor et al. 2004; Krogan et al. 2003; Lin et al. 2020; Mizuguchi et al. 2004). In yeast, the key ATPase component of SWR1 is the protein Swr1, encoded by the *SWR1* gene, and in this review, SWR1 (the complex) and Swr1 (the protein) are used interchangeably. SWR1 is preferentially localized at the NDR which is adjacent to the + 1 nucleosome (Ranjan et al. 2013; Yen et al. 2013). Here, it catalyzes a histone dimer exchange reaction in which each of the two H2A–H2B dimers in the adjacent nucleosome is sequentially replaced with an H2A.Z–H2B dimer (Luk et al. 2010; Sun et al. 2020). However, the picture is likely to be somewhat more complicated based on an analysis of the types of promoters H2A.Z is found at, the relationship of H2A.Z and SWR1 recruitment to one another, and the relationship of H2A.Z incorporation to transcription. A recent study (Bagchi et al. 2020) analyzed H2A.Z occupancy in relation to transcription initiation sites as measured by the technique of SMORE-seq, which is specific for transcripts with capped 5′ ends and thus defines TSS positions more accurately than standard RNA-seq. SMORE-seq is also more sensitive than standard RNA-seq in its ability to detect non-coding RNA that is transcribed in the opposite sense from a normal promoter—what may be termed upstream antisense non-coding RNAs (UAN RNAs) at promoters (Park et al. 2014).

At divergently transcribed genes (Fig. 1d), SWR1 is presumably recruited to the central NDR and incorporates H2A.Z into each of the two flanking nucleosomes which are both "+ 1", with equal propensity as evidenced by the similar H2A.Z occupancy at the flanking nucleosomes. On the other hand, in tandemly oriented genes, the 5′ end of a gene and its promoter abuts the 3′ end of the adjacent gene (Fig. 1d). At these genes, H2A.Z is present at the + 1 nucleosome on the downstream gene, but at the upstream "− 1" nucleosome, the extent of H2A.Z occupancy is proportional to transcription of the UAN RNA. When there is little to no UAN RNA transcribed, there is little to no H2A.Z incorporation into the upstream − 1 nucleosome (Fig. 1d) (Bagchi et al. 2020). Thus, at tandem genes, the − 1 H2A.Z-containing nucleosome is in fact a + 1 nucleosome for an antisense non-coding transcript that is initiated in the opposite direction. At least in yeast, therefore, it is erroneous to consider H2A.Z as occupying a "− 1" nucleosome or flanking the NDR. This revised picture of H2A.Z occupancy is not fully explained by a simple model where SWR1 recruitment to an NDR results in H2A.Z incorporation into the nearest nucleosome, because there is a clear difference in H2A.Z occupancy depending upon whether transcription occurs in that direction. When there is no transcription in the upstream direction to a given gene's TSS, as in case of a tandem gene

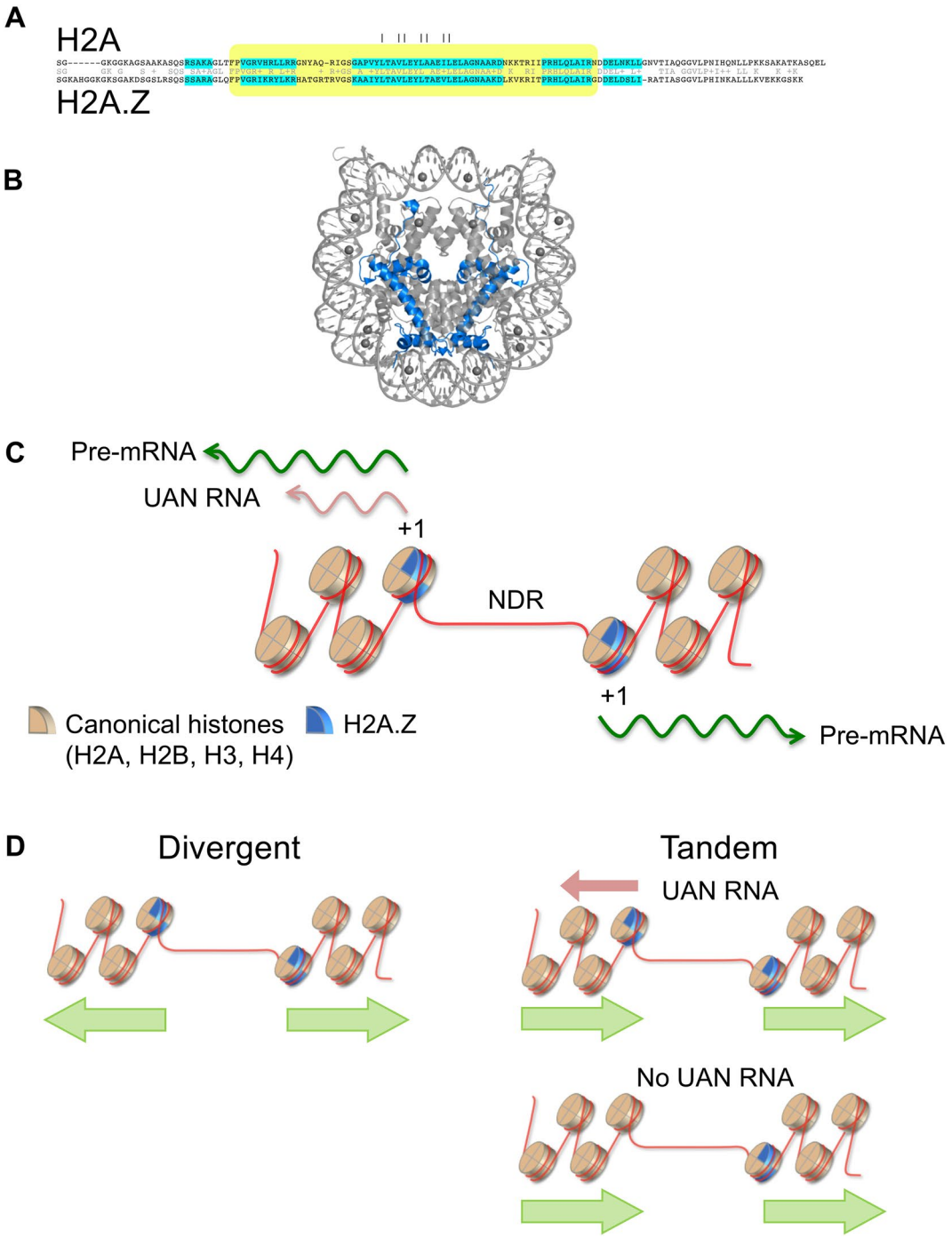

Fig. 1 H2A.Z nucleosome structure and occupancy at yeast promoters. **a** Alignment of yeast H2A and H2A.Z protein sequences. The histone-fold domain and its α-helical segments are indicated by yellow and turquoise highlighting, respectively. Residues involved in interaction of H2A or H2A.Z with H2B are indicated by the bars above. **b** Structure of a nucleosome containing H2A.Z. This representation of the crystal structure of the nucleosome core particle was obtained from PDBe (ebi.ac.uk/pdbe/entry/pdb/1f66) and is a composite structure containing mouse H2A.Z, canonical histones from Xenopus and a DNA sequence from human (Suto et al. 2000). The two H2A.Z polypeptide chains are highlighted in blue. **c** H2A.Z nucleosomes at the promoter of a gene being transcribed left to right. NDR is the nucleosome-depleted region, typically present upstream of the transcription start site. The H2A.Z-containing nucleosome is the + 1 nucleosome in the direction of transcription initiation, either of a divergent coding mRNA or a short upstream antisense noncoding RNA (UAN RNA) (Bagchi et al. 2020). In this depiction, the UAN RNA is antisense relative to the gene on the right. **d** H2A.Z occupancy at the apparent − 1 nucleosome relative to the gene on the right depends on the arrangement of genes on the chromosome and whether a UAN RNA is transcribed

without a UAN, there is no H2A.Z occupancy of the "− 1" nucleosome either. A few additional observations also compel a reevaluation of the notion that simply recruiting SWR1 to the NDR suffices to explain the occupancy of H2A.Z at the flanking nucleosomes (Bagchi et al. 2020). First, there is little quantitative correlation between the strength of Swr1 binding to the NDR and the extent of H2A.Z occupancy of the + 1 nucleosome, as measured by the strength of their ChIP signals. Second, Swr1 binding at NDRs is indistinguishable between tandem and divergent genes, whereas H2A.Z incorporation at the upstream + 1 nucleosome is markedly higher for divergent genes. Finally, Swr1 binding to the NDR is itself dependent to a certain extent on H2A.Z; in the absence of H2A.Z in the genome, Swr1 binding at its most prominent sites is reduced (Bagchi et al. 2020). In particular, the strong directionality coinciding with transcriptional activity in terms of H2A.Z incorporation into the + 1 nucleosome suggests that a transcription-related process could contribute to this directionality.

Links between H2A.Z occupancy and transcription

What is the link between transcription and H2A.Z occupancy? One potential link comes from the finding that replacement of H2A.Z at the + 1 nucleosome in vivo seems to coincide with the assembly and function of the PIC (Ranjan et al. 2020; Tramantano et al. 2016; Zanton and Pugh 2006). Eviction of H2A.Z, namely, replacement of H2A.Z–H2B dimers by H2A–H2B dimers can be catalyzed in vitro by the INO80 complex, also an ATP-dependent chromatin remodeler which can, in effect, reverse the action of the SWR1 complex (Papamichos-Chronakis et al. 2011; Watanabe et al. 2013). Experiments testing a genome-wide role in vivo for INO80 in evicting H2A.Z from nucleosomes have, however, revealed conflicting results. While some studies have reported a requirement for either Ino80 or Arp5, both key components of the INO80 complex, in regulating H2A.Z occupancy at promoters and its eviction (Papamichos-Chronakis et al. 2011; Yen et al. 2013), other studies have reported contrasting results (Jeronimo et al. 2015; Tramantano et al. 2016). Moreover, depletion of components of the general transcription machinery such as TBP (the TATA binding protein), RNAPII, or the RNAPII C-terminal domain kinase Kin28, results in accumulation of H2A.Z at + 1 nucleosomes or on chromatin, strongly suggesting a role for the PIC or transcription initiation itself in evicting H2A.Z (Ranjan et al. 2020; Tramantano et al. 2016).

Another link between transcription and H2A.Z occupancy could arise from the fact that Bdf1, a bromodomain-containing component of the SWR1 complex, is shared with TFIID, the member of the general transcription machinery that also contains TBP (Krogan et al. 2003; Matangkasombut et al. 2000; Schier and Taatjes 2020). Indeed, SWR1 recruitment to promoters is facilitated by interaction of the Bdf1 bromodomain with acetylated histones H2A, H3, and H4 (Altaf et al. 2010; Koerber et al. 2009; Ladurner et al. 2003; Matangkasombut and Buratowski 2003; Raisner et al. 2005). Bdf1 occupancy is strongest at the + 1 and to a lesser extent, the + 2 nucleosome (Koerber et al. 2009). However, Bdf1 occupancy does not correlate well with SWR1 and H2A.Z at all genes, whereas it does correlate highly with Taf1, a component of TFIID (Joo et al. 2017). Bdf1 is part of the TAF (TBP associated factor) complex that is detectable downstream of the core promoter, where it serves to reinitiate transcription at strongly TAF-dependent genes. It has been proposed that in this manner, Bdf1 could be left behind after reinitiation and if so, it may serve to recruit the SWR1 complex and promote H2A.Z incorporation at the + 1 nucleosome (Joo et al. 2017). Bdf1-dependent enhancement of SWR1 function at the + 1 nucleosome could thus contribute to the transcription-dependent directionality of H2A.Z incorporation at the promoter, although such a mechanism remains to be shown. H2A.Z could represent a signpost of transcription having occurred through a + 1 nucleosome at some point, while at the same time showing no strong correlation with the extent of transcription as measured by steady-state RNA levels or rates of transcription measured indirectly by RNAPII Ser-5P occupancy (Bagchi et al. 2020).

Ribosomal protein gene promoters lack H2A.Z

The ribosomal protein (RP) genes in yeast call for special consideration. These genes are actively transcribed during normal growth conditions and tend to have relatively long NDRs, which would make them ideal candidates for SWR1 occupancy and H2A.Z incorporation. However, although they show high levels of Bdf1 (and TAF) occupancy, they show much lower levels of Swr1 at their NDR and virtually no H2A.Z at their clearly distinguishable + 1 nucleosome, so much so that the RP genes are the clear outliers in the entire yeast genome with regard to Swr1 and H2A.Z occupancy (Bagchi et al. 2020; Rhee et al. 2014; Zhang et al. 2005). While the explanation for this is not entirely clear, it could reflect in part the fact that the extent of H2A.Z occupancy at a + 1 nucleosome is a function not just of its incorporation by SWR1, but also its eviction and replacement by H2A. At RP genes, the low levels of SWR1 combined with rapid replacement due to highly active transcription could result in very low levels of steady-state H2A.Z occupancy. Interestingly, in the absence of H2A.Z, Ino80 accumulates specifically at RP genes which suggests that it might contribute to H2A.Z replacement there under

normal circumstances. Nevertheless, there is no accumulation of H2A.Z at RP genes in the absence of Ino80 (Bagchi et al. 2020; Tramantano et al. 2016).

As noted above, depletion of TBP results in an increase of H2A.Z occupancy at + 1 nucleosomes at most genes. Depletion of Rpb1 (the large subunit of RNAPII) similarly increases H2A.Z occupancy at most + 1 nucleosomes (Tramantano et al. 2016), and interestingly, also leads to increased downstream binding of the reinitiating form of the TAF complex that contains Bdf1 (Joo et al. 2017). Could the apparent requirement for the PIC for H2A.Z eviction reflect an increase in H2A.Z incorporation following PIC depletion due to additional Swr1 recruited by residual Bdf1 left behind after reinitiation by the TAF complex? At least at two promoters that were tested, *SWR1* itself and *FUN12*, which are sites of high Swr1 binding, depletion of TBP caused a decrease in Swr1 occupancy (Tramantano et al. 2016), suggesting that the PIC depletion does not lead to increased H2A.Z incorporation. However, at the majority of the genes in the genome, it remains to be shown that there is no increase in SWR1 recruitment possibly mediated by Bdf1 upon PIC depletion. At RP genes, TBP depletion causes an increase in H2A.Z occupancy but depletion of Rbp1 does not (Tramantano et al. 2016). Notably, depletion of Rpb1 also does not cause an increase of Taf1 binding (and, one infers, Bdf1) but rather, leads to a decrease of Taf1 specifically at RP genes (Joo et al. 2017). Thus, the increase in H2A.Z occupancy at RP genes was seen only when TBP was depleted, but not when Rpb1 was depleted, again underscoring the possibility of distinct mechanisms prevailing at these promoters.

In summary, H2A.Z occupancy of nucleosomes at yeast promoters is observed primarily at the first nucleosome in the direction of transcription and reflects a balance between incorporation by the SWR1 complex and eviction by transcriptional activity, possibly abetted by other chromatin remodelers or chaperones. The extent of H2A.Z at the + 1 nucleosome is not correlated with the amount of bound SWR1 or the extent of transcriptional activity, with ribosomal protein genes forming a distinct class showing strong transcriptional activity and low H2A.Z. Further studies that quantify the contributions of each of these factors to H2A.Z occupancy at different classes of promoters and other locations will shed light on the role of this universal histone variant in the yeast genome and will undoubtedly guide similar studies and generate insights in other eukaryotes.

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