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Patterning chromatin: form and function for H2A.Z variant nucleosomes

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Although many histone variants are specific to higher eukaryotes, the H2A variant H2A.Z has been conserved during eukaryotic evolution. Genetic studies have demonstrated roles for H2A.Z in antagonizing gene-silencing, chromosome stability and gene activation. Biochemical work has identified a conserved chromatin-remodeling complex responsible for H2A.Z deposition. Recent studies have shown that two H2A.Z nucleosomes flank a nucleosome-free region containing the transcription initiation site in promoters of both active and inactive genes in *Saccharomyces cerevisiae*. This chromatin pattern is generated through the action of a DNA deposition signal and a specific pattern of histone tail acetylation.

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Introduction

The two major classes of chromatin are euchromatin and heterochromatin, terms that were originally coined to describe the morphology of chromosomes in *Drosophila*. Despite significant progress in identifying the proteins and modifications involved in the formation of heterochromatin, the mechanism by which these factors lead to the properties of heterochromatin is not known. Even less is known about how euchromatin is specified. One mechanism that promotes the euchromatic state is the substitution of H2A for the variant H2A.Z. This review focuses on this molecule and the rapid advances in our understanding of its localization, deposition mechanisms, and functions.

H2A.Z is conserved across eukaryotes

Of the core histone subunits, variants of H2A are particularly common. There are five major H2A-type histones [1]. Canonical H2A is the most abundant form; its expression and deposition are coupled to replication. H2A.X is

involved in the response to DNA damage. MacroH2A is involved in constitutive heterochromatin and transcriptional silencing [2]. Another variant, H2ABbd, named for its relative depletion from Barr bodies in mammals, remains relatively uncharacterized [3]. H2A.Z, which is sometimes referred to as H2A.Z/F, is the most conserved variant — it is found in organisms as diverse as the early branching eukaryote *Plasmodium falciparum* (J DeRisi, personal communication) to humans. Table 1 lists H2A variants found in commonly studied species. In some cases, two H2A-types exist as a single, bi-functional molecule; for example, the *S. cerevisiae* H2A also functions as H2A.X [4].

H2A.Z homologs are more similar across species than is canonical H2A. Characterized H2A.Z-type variants include H2A.Z in mammals, *C. elegans* and fungi [5,6]; H2Av, a bi-functional H2A.Z/H2A.X variant in *Drosophila* [7]; H2Ahv1 in *Tetrahymena* [8]; H2A.F in birds [9]; and H2A.Z/F in sea urchins [10]. The strong conservation of H2A.Z among species probably reflects common and important functions.

Insights from the atomic resolution structure of the H2A.Z variant nucleosome

The core region of the H2A.Z variant differs significantly from that of H2A. Three conserved residues that differ between H2A and H2A.Z are of particular note. The crystal structure of a *Xenopus laevis* H2A.Z nucleosome was solved by Suto *et al.* [11] and revealed a difference in the (H3–H4)₂ tetramer docking domain between the H2A subunits (residues 81–119 in H2A). Specifically, the substitution of glutamine (Gln 104 in H2A) to glycine (Gly 106 in H2A.Z) results in the loss of three hydrogen bonds, which is predicted to cause a subtle destabilization of the H2A.Z–H3 interaction. Additionally, the histidine (His 112) residue on the surface of the H2A.Z histone octamer binds to a metal ion, and this interaction may be stabilized by the nearby His 114 residue. This ion might provide a unique surface for protein interaction. Finally, H2A.Z–H2B dimers display on the surface of the histone octamer an extended acidic patch that may be important for making contacts with adjacent H4 tails or non-histone protein factors.

Physical properties of H2A.Z nucleosomes

In vitro studies have characterized various biochemical properties of nucleosomes containing H2A.Z. Reconstituted nucleosomes bearing H2A.1 or H2A.Z from humans display differences in electrophoretic mobility, and in sedimentation values under varying salt conditions

Table 1

Commonly used names for H2A variants across species.

H2A Class	Protists	Fungi			Metazoans			
	Ciliate	Yeast	Nematode	Fly	Fish	Amphibian	Bird	Mammal
Canonical	H2A	H2A	H2A	H2A	H2A	H2A	H2A	H2A
H2A.Z	H2Ahv1	H2A.Z	H2AZ	H2Av	H2A.Z	H2A.Z	H2A.F	H2AZ
H2A.X	–	H2A	–	H2Av	–	H2A.X	H2A.X	H2A.X
MacroH2A	–	–	–	–	MacroH2A	mH2A	mH2A	MacroH2A
H2ABbd	–	–	–	–	–	–	–	H2ABbd

– Indicates either that no protein exists or that a homolog has yet to be reported.

[12]. Fluorescence resonance energy transfer (FRET)-based assays with *Xenopus laevis* core histones and mouse H2A.Z revealed that H2A.Z–H2B dimers dissociate more slowly in salt conditions than do canonical H2A–H2B dimers [13], the opposite of what was observed in earlier studies that used different methods. However, it was also reported that H2A.Z nucleosomes display a lower melting temperature than canonical nucleosomes [14]. In purified yeast chromatin, H2A.Z can be released from nucleosomes by treatment with a lower concentration of sodium chloride salt than concentrations required to release either H2A or H3 [15**]. It seems likely that many of the different conclusions among these studies are caused by differences in the sources of chromatin, and by the methodology used to define the stability of H2A.Z–H2B dimers. Further work seems necessary to clarify the physical properties of H2A.Z nucleosomes and their potential relevance to the biological functions of H2A.Z.

The deposition pattern of H2A.Z nucleosomes

Early studies of hv1, an H2A.Z-type variant in the ciliate *Tetrahymena* species, showed that it preferentially associates with the transcriptionally active macronucleus rather than with the silent micronucleus [16]. This distribution was proposed to be consistent with a role in transcriptional activation.

Genome-scale studies of budding yeast *Saccharomyces cerevisiae* have demonstrated H2A.Z deposition at the vast majority of gene promoters in euchromatin, but a depletion from silenced regions such as subtelomeric domains [15**,17**,18**]. Most strikingly, H2A.Z generally occupies single nucleosomes upstream and downstream of a nucleosome-free region that encompasses the transcription initiation site of most genes (Figure 1). Remarkably, a short 22 bp sequence from a promoter was shown to be sufficient to promote both the formation of a nucleosome-free region and the deposition of H2A.Z in the two flanking nucleosomes [17**]. This sequence consists of a binding site for the Myb-related DNA binding protein Reb1 and an adjacent dT:dA tract, and both motifs are required for H2A.Z deposition. Both these sequence elements are commonly found in yeast promoters; indeed, the Reb1 site is the most conserved element of yeast promoters, its degree of sequence conservation

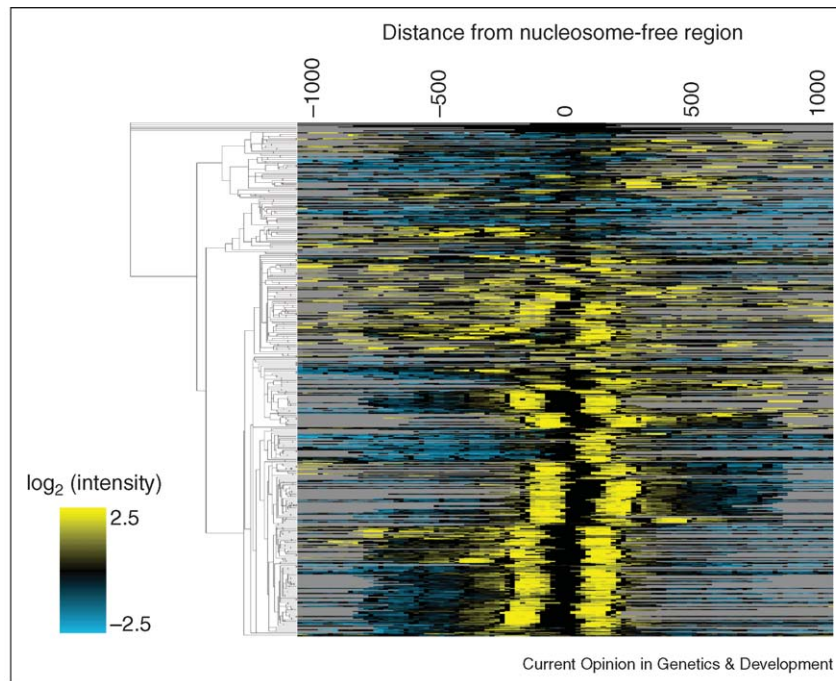
among species exceeding that of the TATA box. Thus, there exists a DNA signal for H2A.Z deposition.

The *Drosophila melanogaster* H2A.Z homolog, H2Av, is not confined to euchromatin: immunofluorescence studies demonstrated that H2Av occurs in heterochromatic chromocenters as well as throughout the arms of polytene chromosomes [7]. H2Av distribution was further compared with that of RNA polymerase II, and, although the two patterns partially overlapped, H2Av was also found at loci where no detectable Pol II was present, which suggests the presence of H2Av at inactive genes. Chromatin immunoprecipitation (ChIP) experiments showed that H2Av is present at various loci such as constitutively active genes — both the un-induced and the induced forms of genes — as well as transcriptionally inactive loci. H2Av also functions as an H2A.X [19]; therefore, some of its observed localization pattern may be due to its other identity.

A recent study of H2A.Z localization in chicken erythrocytes showed an association of H2A.Z with the 5' ends of several genes assayed by ChIP [20**]. Remarkably, in the β -globin locus, the well-characterized 5' insulator that flanks a heterochromatic region is highly enriched for H2A.Z. This finding is consistent with studies in yeast that show that H2A.Z antagonizes heterochromatin spread (see below). If H2A.Z nucleosomes generally closely flank heterochromatic regions, could cytological data showing concentrations of H2A.Z in heterochromatin actually reflect its enrichment in flanking nucleosomes?

Different mammalian cell types show distinct cytological patterns of H2A.Z localization. In mouse embryos, H2A.Z displays diffuse staining but is concentrated at pericentric chromatin. However, it is selectively depleted from constitutive heterochromatin such as that of the inactive X chromosome. H2A.Z is not present before differentiation of totipotent cells early in development, suggesting that it is not required for early transcriptional programs [21]. In cultured monkey COS-7 cells, H2A.Z is, in fact, depleted from centromeric heterochromatin and is found associated with chromosome arms [22*]. Some concentration in heterochromatic 'knobs' on chromosome arms was also observed.

Figure 1



High-resolution mapping of H2A.Z nucleosomes in *S. cerevisiae*. Clustered view of tiled microarray array data centered on nucleosome-free regions. Each row represents a single promoter region, and each column corresponds to data from a particular microarray spot. H2A.Z levels are normalized for nucleosome density. See Raisner *et al.* [17**] for further details.

A conserved chromatin-remodeling complex that deposits H2A.Z

In *S. cerevisiae*, H2A.Z is deposited in chromatin by the 13-subunit Swr1-C remodeling complex [23**,24,25*]. The catalytic subunit, Swr1, is homologous to members of the SWI-SNF family of ATP-dependent chromatin-remodeling enzymes. The Bdf1 subunit contains tandem bromodomains that have been shown to specifically bind the acetylated tails of histones H3 and H4. Both histone tail acetylation and Bdf1 are important for H2A.Z targeting and deposition in promoter regions. Swr1-C has four subunits — Swc4, Yaf9, Arp4, and actin — that are also components of the NuA4 histone acetyltransferase complex. Swr1-C also shares components with the Ino80-C remodeling complex, namely, Arp1, actin, Rvb1 and Rvb2. There are also six subunits unique to Swr1-C.

The Tip60 complex, the *Drosophila* homolog of Swr1-C, deposits H2Av [26**]. Each subunit of the Tip60 complex has a homologous subunit in the human SRCAP (SNF2-related CBP activator protein) complex [27*]. As with SRCAP, each subunit has a homolog in *S. cerevisiae* (Table 2). The Tip60 and SRCAP complexes appear to be a fusion of the Swr1 and NuA4 complexes of yeast (Table 2). This organization is consistent with the established role for histone H4 tail acetylation in H2A.Z deposition in *S. cerevisiae*. Indeed, the Tip60 complex acetylates nucleosomes, and this acetylation is important

for replacement of phosphorylated H2Av with unphosphorylated H2Av at the sites of DNA lesions. Given the complete conservation of all the subunits of Swr1-C in the Tip60 and SRCAP complexes, it is likely that the fundamental molecular mechanisms of targeting and replacing H2A.Z are also conserved.

Functions for H2A.Z: anti-silencing, transcription and centromere function

Several studies over the past five years have examined specific roles for H2A.Z in transcription in *S. cerevisiae*. Early work by Smith and colleagues showed that cells harboring a null mutation in *HTZ1*, the gene encoding H2A.Z, display defects in the induction of the *PHO5* and *GAL1* genes when combined with null mutations in genes encoding the chromatin-remodeling enzyme Snf2-Swi2 or Sin1, an HMG (high mobility group)-like protein [28]. No transcriptional defect was observed for several other genes. Subsequent studies of H2A-H2A.Z chimeric genes showed that *GAL1* and *GAL10* gene activation was specifically dependent upon the C-terminal domain of H2A.Z [29], consistent with earlier analysis of chimeric H2Av-H2A genes in *Drosophila*. Pull-down experiments using crude extracts demonstrated an association between the H2A.Z C-terminal domain and RNA polymerase II (Rpb1). A defect in the ability of Rpb1 to bind *in vivo* to the *GAL1* promoter was observed when an *htz1* Δ strain was shifted to galactose medium. It has been shown

Table 2**List of the H2A.Z chromatin-remodeling complexes for budding yeast, fly and human.**

Yeast Swr1-C	Yeast NuA4	Fly Tip60	Human SRCAP	Comment
Rvb1		dPontin	Pontin	
Rvb2		dReptin	Reptin	
Arp4		BAP55	Baf53a	Actin-related
Eaf7		dMrgB	MrgBP	
Swc4 (Eaf2, God1)		dDMA	DMAP1	
Bdf1		dBrd8	Brd8/TRCp12	Bromodomain protein
Act1		Act87E	Actin	Actin
Yaf9		dGas41	Gas41	
Swr1 [*]		Domino	p400	SWI-SNF ATPase
Swc2 (Vps72)		dYL-1	YL-1	
H2A/H2A.Z		H2Av	H2A.Z/H2A.X	
H2B		H2B	H2B	
Swc3 (Alr1)				
Swc5 (Aor1)				
Swc6 (Vps71)				
Swc7 (Aws1)				
	Eaf1 [*]	Domino	p400	
	Eaf3	dMrg15	Mrg15	Chromodomain protein
	Epl1	E(Pc)	Epc1	
	Esa1	dTip60	Tip60	Histone acetylation
	Tra1	dTra1	TRRAP	
	Yng2	dIng3~	Ing3	ING family
	Eaf6	dEaf6	FLJ11730	

Note for yeast, the NuA4 subunits share homology with those of the Tip60 and SRCAP complexes but do not co-purify with Swr1-C. ^{*} Indicates that the Domino-p400 subunits are actually a fusion of Swr1 and Eaf1 from yeast.

recently that at the *GAL1* gene promoter, the nucleosome positioned immediately downstream of the transcription initiation site, shifts downstream by approximately 20 bp in an *htz1Δ* strain [18^{**}], perhaps contributing to the defective Rpb1-binding. In addition to the dependence of *GAL1* and *GAL10* on H2A.Z for full activation, it has also been shown that the cell cycle genes *CLN2* and *CLB5* have H2A.Z at their promoters and require H2A.Z for their timely and full transcriptional activation; consequently, deletion of *HTZ1* results in a delayed progression through S-phase, and reduced cell cycle synchrony [30]. For the vast majority of genes at this point, however, microarray studies have demonstrated only a modest defect in general transcriptional induction in *htz1Δ* cells [31]. Thus, although H2A.Z seems to play a role in transcriptional induction, it appears to be largely redundant with other factors.

By contrast, microarray and ChIP studies in *S. cerevisiae* suggest that the major function for H2A.Z in gene expression is to antagonize gene-silencing. Genes that have H2A.Z-dependent expression cluster near silencing regions. Cells lacking H2A.Z exhibit the ectopic spread of the Sir2–3–4 silencing complex beyond its normal boundaries [31]. Its localization in promoter regions of genes in euchromatin, and its exclusion from heterochromatin places it at an appropriate site to protect genes from silencing. The fact that genes need not be transcribed for H2A.Z deposition to occur is consistent with this function for H2A.Z.

In metazoans, null mutations in H2A.Z yield lethal phenotypes across a range of species, including *Drosophila* and mouse [32,33]. *Drosophila* H2Av mutants show a defect in heterochromatin formation [34]. Moreover, H2Av was recruited to the location of a silenced transgene array, suggesting a direct role of this hybrid variant in silencing. In *Xenopus laevis*, either RNA interference (RNAi) of H2A.Z or expression of dominant alleles results in developmental defects [35^{*}]. Whether these defects are caused by defects in transcriptional regulation is unclear.

In *Schizosaccharomyces pombe*, *S. cerevisiae* and cultured mammalian cells, knockout or depletion of H2A.Z results in increased rates of chromosome loss [6,22^{*}]. In principle, this phenotype could be a result of indirect effects of H2A.Z loss on the expression of factors important for chromosome segregation; however, it is more likely to be a reflection of a direct role for H2A.Z in centromere function. Indeed, it has been reported that the mouse H2A.Z protein interacts with the kinetochore component INCENP (inner centromere protein) [21].

Euchromatin and heterochromatin: yin and yang

In *S. cerevisiae*, two features of chromatin contribute to the deposition of H2A.Z in euchromatin: a DNA signal and histone tail acetylation [15^{**},17^{**}]. Heterochromatin formation in yeast is also nucleated by specific DNA signals but is propagated by histone tail de-acetylation

rather than histone tail acetylation [36]. One apparent difference is that H2A.Z does not appear to spread to coat regions of the chromosome in yeast but is generally restricted to promoter regions. Nonetheless, these recent results suggest that euchromatin and heterochromatin may be two sides of the same coin. An intriguing property of heterochromatin is its ability to template its own propagation. Whether the same is true of euchromatin is an interesting question for future investigation.

Update

Recently, Wu *et al.* [37] reported that Swc2, a conserved subunit of Swr1-C, directly binds to H2A.Z. Also, Li *et al.* [38] described genome-wide localization patterns of H2A.Z and reported that the lack of H2A.Z did not affect nucleosome position at several loci.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Thatcher TH, Gorovsky MA: **Phylogenetic analysis of the core histones H2A, H2B, H3, and H4.** *Nucleic Acids Res* 1994, **22**:174-179.
 2. Costanzi C, Pehrson JR: **Histone macroH2A1 is concentrated in the inactive X chromosome of female mammals.** *Nature* 1998, **393**:599-601.
 3. Gautier T, Abbott DW, Molla A, Verdel A, Ausio J, Dimitrov S: **Histone variant H2ABbd confers lower stability to the nucleosome.** *EMBO Rep* 2004, **5**:715-720.
 4. Redon C, Pilch DR, Rogakou EP, Orr AH, Lowndes NF, Bonner WM: **Yeast histone 2A serine 129 is essential for the efficient repair of checkpoint-blind DNA damage.** *EMBO Rep* 2003, **4**:678-684.
 5. Jackson JD, Gorovsky MA: **Histone H2A.Z has a conserved function that is distinct from that of the major H2A sequence variants.** *Nucleic Acids Res* 2000, **28**:3811-3816.
 6. Carr AM, Dorrington SM, Hindley J, Phear GA, Aves SJ, Nurse P: **Analysis of a histone H2A variant from fission yeast: evidence for a role in chromosome stability.** *Mol Gen Genet* 1994, **245**:628-635.
 7. Leach TJ, Mazzeo M, Chotkowski HL, Madigan JP, Wotring MG, Glaser RL: **Histone H2A.Z is widely but nonrandomly distributed in chromosomes of *Drosophila melanogaster*.** *J Biol Chem* 2000, **275**:23267-23272.
 8. Allis CD, Richman R, Gorovsky MA, Ziegler YS, Touchstone B, Bradley WA, Cook RG: **hv1 is an evolutionarily conserved H2A variant that is preferentially associated with active genes.** *J Biol Chem* 1986, **261**:1941-1948.
 9. Harvey RP, Whiting JA, Coles LS, Krieg PA, Wells JR: **H2A.F: an extremely variant histone H2A sequence expressed in the chicken embryo.** *Proc Natl Acad Sci USA* 1983, **80**:2819-2823.
 10. Ernst SG, Miller H, Brenner CA, Nocente-McGrath C, Francis S, McIsaac R, Harvey RP, Whiting JA, Coles LS, Krieg PA *et al.*: **Characterization of a cDNA clone coding for a sea urchin histone H2A variant related to the H2A.F/Z histone protein in vertebrates.** *Nucleic Acids Res* 1987, **15**:4629-4644.
 11. Suto RK, Clarkson MJ, Tremethick DJ, Luger K: **Crystal structure of a nucleosome core particle containing the variant histone H2A.Z.** *Nat Struct Biol* 2000, **7**:1121-1124.
 12. Abbott DW, Ivanova VS, Wang X, Bonner WM, Ausio J: **Characterization of the stability and folding of H2A.Z chromatin particles: implications for transcriptional activation.** *J Biol Chem* 2001, **276**:41945-41949.
 13. Park YJ, Dyer PN, Tremethick DJ, Luger K: **A new fluorescence resonance energy transfer approach demonstrates that the histone variant H2AZ stabilizes the histone octamer within the nucleosome.** *J Biol Chem* 2004, **279**:24274-24282.
 14. Flaus A, Rencurel C, Ferreira H, Wiechens N, Owen-Hughes T: **Sin mutations alter inherent nucleosome mobility.** *EMBO J* 2004, **23**:343-353.
 15. Zhang H, Roberts DN, Cairns BR: **Genome-wide dynamics of Htz1, a histone H2A variant that poises repressed/basal promoters for activation through histone loss.** *Cell* 2005, **123**:219-231.
- The authors localize H2A.Z across the yeast genome at the resolution of intergenic regions and open reading frames. A selective enrichment of promoter segments with H2A.Z was found, and this negatively correlated with transcription. On the basis of this observation and the sensitivity of H2A.Z to salt extraction in isolated yeast chromatin, the authors propose that H2A.Z facilitates nucleosome loss during gene induction.
16. Stargell LA, Bowen J, Dadd CA, Dedon PC, Davis M, Cook RG, Allis CD, Gorovsky MA: **Temporal and spatial association of histone H2A variant hv1 with transcriptionally competent chromatin during nuclear development in *Tetrahymena thermophila*.** *Genes Dev* 1993, **7**:2641-2651.
 17. Raisner RM, Hartley PD, Meneghini MD, Bao MZ, Liu CL, Schreiber SL, Rando OJ, Madhani HD: **Histone variant H2A.Z marks the 5' ends of both active and inactive genes in euchromatin.** *Cell* 2005, **123**:233-248.
- Using chromatin immunoprecipitation and high-density tiling microarrays, the authors demonstrate that two H2A.Z nucleosomes flank a nucleosome-free region at the transcription start site of most genes in yeast euchromatin. This localization is dependent upon histone acetylation and Bdf1 but does not require gene transcription. A 22 bp segment containing a binding site for the Myb-related protein Reb1 and an adjacent dA:dT tract was shown to be sufficient to induce a nucleosome-free region flanked by two H2A.Z nucleosomes.
18. Guillemette B, Bataille AR, Gevry N, Adam M, Blanchette M, Robert F, Gaudreau L: **Variant histone H2A.Z is globally localized to the promoters of inactive yeast genes and regulates nucleosome positioning.** *PLoS Biol* 2005, **3**:e384.
- To demonstrate promoter enrichment with H2A.Z, the authors immunoprecipitated sonicated *S. cerevisiae* chromatin with anti-Myc-H2A.Z antibodies and hybridized probes derived from this material to microarrays that contain an oligonucleotide approximately every 300 bp across the genome. Additionally, they used indirect end-labeled micrococcal nuclease-digested DNA to show that there is a small shift in the position of nucleosomes at the *GAL1* promoter in an *htz1Δ* strain.
19. Madigan JP, Chotkowski HL, Glaser RL: **DNA double-strand break-induced phosphorylation of *Drosophila* histone variant H2Av helps prevent radiation-induced apoptosis.** *Nucleic Acids Res* 2002, **30**:3698-3705.
 20. Bruce K, Myers FA, Mantouvalou E, Lefevre P, Greaves I, Bonifer C, Tremethick DJ, Thorne AW, Crane-Robinson C: **The replacement histone H2A.Z in a hyperacetylated form is a feature of active genes in the chicken.** *Nucleic Acids Res* 2005, **33**:5633-5639.
- The authors use chromatin immunoprecipitation for both acetylated and unacetylated forms of H2A.Z in chicken to show that the 5' ends of both tissue-specific and housekeeping genes are selectively enriched with the acetylated form. Notably, the β -globin insulator element is highly enriched with acetylated H2A.Z.
21. Rangasamy D, Berven L, Ridgway P, Tremethick DJ: **Pericentric heterochromatin becomes enriched with H2A.Z during early mammalian development.** *EMBO J* 2003, **22**:1599-1607.

22. Rangasamy D, Greaves I, Tremethick DJ: **RNA interference demonstrates a novel role for H2A.Z in chromosome segregation.** *Nat Struct Mol Biol* 2004, **11**:650-655.

The authors use an inducible RNAi system to demonstrate that H2A.Z is required for proper segregation of chromosomes in mammalian cells.

23. Mizuguchi G, Shen X, Landry J, Wu WH, Sen S, Wu C: **ATP-driven exchange of histone H2AZ variant catalyzed by SWR1 chromatin remodeling complex.** *Science* 2004, **303**:343-348.

The authors demonstrate using *in vitro* and *in vivo* assays that a complex containing the Swi2/Snf2-related ATPase Swr1 is responsible for H2A.Z deposition in yeast.

24. Krogan NJ, Keogh MC, Datta N, Sawa C, Ryan OW, Ding H, Haw RA, Pootoolal J, Tong A, Canadien V *et al.*: **A Snf2 family ATPase complex required for recruitment of the histone H2A variant Htz1.** *Mol Cell* 2003, **12**:1565-1576.

25. Kobor MS, Venkatasubrahmanyam S, Meneghini MD, Gin JW, Jennings JL, Link AJ, Madhani HD, Rine J: **A protein complex containing the conserved Swi2/Snf2-related ATPase Swr1p deposits histone variant H2A.Z into euchromatin.** *PLoS Biol* 2004, **2**:E131.

The authors purify the 13-subunit Swr1-C in yeast and demonstrate that it is required for *in vivo* deposition of H2A.Z.

26. Kusch T, Florens L, Macdonald WH, Swanson SK, Glaser RL, Yates JR III, Abmayr SM, Washburn MP, Workman JL: **Acetylation by Tip60 is required for selective histone variant exchange at DNA lesions.** *Science* 2004, **306**:2084-2087.

The authors demonstrate that the *Drosophila* Tip60 complex is responsible for acetylation and exchange of the phosphorylated H2Av histone variant with unphosphorylated H2Av at sites of DNA lesions.

27. Cai Y, Jin J, Florens L, Swanson SK, Kusch T, Li B, Workman JL, Washburn MP, Conaway RC, Conaway JW: **The mammalian YL1 protein is a shared subunit of the TRRAP/TIP60 histone acetyltransferase and SRCAP complexes.** *J Biol Chem* 2005, **280**:13665-13670.

The authors purify a mammalian presumptive H2A.Z deposition complex and show that it has subunits homologous to those in the yeast Swr1-C and *Drosophila* Tip60 complexes.

28. Santisteban MS, Kalashnikova T, Smith MM: **Histone H2A.Z regulates transcription and is partially redundant with nucleosome remodeling complexes.** *Cell* 2000, **103**:411-422.

29. Adam M, Robert F, Laroche M, Gaudreau L: **H2A.Z is required for global chromatin integrity and for recruitment of RNA polymerase II under specific conditions.** *Mol Cell Biol* 2001, **21**:6270-6279.

30. Dhillon N, Oki M, Szyjka SJ, Aparicio OM, Kamakaka RT: **H2A.Z functions to regulate progression through the cell cycle.** *Mol Cell Biol* 2006, **26**:489-501.

31. Meneghini MD, Wu M, Madhani HD: **Conserved histone variant H2A.Z protects euchromatin from the ectopic spread of silent heterochromatin.** *Cell* 2003, **112**:725-736.

32. van Daal A, Elgin SC: **A histone variant, H2AvD, is essential in *Drosophila melanogaster*.** *Mol Biol Cell* 1992, **3**:593-602.

33. Faast R, Thonglairoam V, Schulz TC, Beall J, Wells JR, Taylor H, Matthaai K, Rathjen PD, Tremethick DJ, Lyons I: **Histone variant H2A.Z is required for early mammalian development.** *Curr Biol* 2001, **11**:1183-1187.

34. Swaminathan J, Baxter EM, Corces VG: **The role of histone H2Av variant replacement and histone H4 acetylation in the establishment of *Drosophila* heterochromatin.** *Genes Dev* 2005, **19**:65-76.

35. Ridgway P, Brown KD, Rangasamy D, Svensson U, Tremethick DJ: **Unique residues on the H2A.Z containing nucleosome surface are important for *Xenopus laevis* development.** *J Biol Chem* 2004, **279**:43815-43820.

Using immunofluorescence, RNAi and mutant alleles, the authors show that H2A.Z is localized in a tissue-specific manner and is required for proper *Xenopus laevis* development.

36. Rusche LN, Kirchmaier AL, Rine J: **The establishment, inheritance, and function of silenced chromatin in *Saccharomyces cerevisiae*.** *Annu Rev Biochem* 2003, **72**:481-516.

37. Wu WH, Alami S, Luk E, Wu CH, Sen S, Mizuguchi G, Wei D, Wu C: **Swc2 is a widely conserved H2AZ-binding module essential for ATP-dependent histone exchange.** *Nat Struct Mol Biol* 2005, **12**:1064-1071.

38. Li B, Pattenden SG, Lee D, Gutierrez J, Chen J, Seidel C, Gerton J, Workman JL: **Preferential occupancy of histone variant H2AZ at inactive promoters influences local histone modifications and chromatin remodeling.** *Proc Natl Acad Sci USA* 2005, **102**:18385-18390.

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