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Review

Precise deposition of histone H2A.Z in chromatin for genome expression and maintenance☆

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ABSTRACT

Histone variant H2A.Z is essential in higher eukaryotes and has different functions in the cell. Several studies indicate that H2A.Z is found at specific loci in the genome such as regulatory-gene regions, where it poises genes for transcription. Its deposition creates chromatin regions with particular structural characteristics which could favor rapid transcription activation. This review focuses on the highly regulated mechanism of H2A.Z deposition in chromatin which is essential for genome integrity. Chaperones escort H2A.Z to large ATP-dependent chromatin remodeling enzymes which are responsible for its deposition/eviction. Over the last ten years, biochemical, genetic and genomic studies helped us understand the precise role of these complexes in this process. It has been suggested that a cooperation occurs between histone acetyltransferase and chromatin remodeling activities to incorporate H2A.Z in chromatin. Its regulated deposition near centromeres and telomeres also shows its implication in chromosomal structure integrity and parallels a role in DNA damage response. The dynamics of H2A.Z deposition/eviction at specific loci was shown to be critical for genome expression and maintenance, thus cell fate. Altogether, recent findings reassert the importance of the regulated deposition of this histone variant. This article is part of a Special Issue entitled: Histone chaperones and Chromatin assembly.

1. Introduction

To maintain stability and integrity of the genome, eukaryotic DNA is organized in a highly regulated structure called chromatin. DNA molecules are bound by highly conserved proteins providing structural support to control important functions of the genome. Chromatin is a repetition of nucleosomes formed by 146 bp of DNA wrapped around an octamer of proteins composed of two copies of each canonical histone H3, H4, H2A and H2B [1]. The chromatin assembly model implies two steps. First, a core (H3/H4)2 tetramer is assembled, and then, two H2A/H2B dimers associate separately with the tetramer to form the histone octamer [2]. Histones are small basic proteins that contain a core globular domain and a positively charged flexible N-terminal tail. Several amino acids on the tails can be modified by post-translational modifications and different combinations of these have been proposed to form an epigenetic code [3]. These signatures direct gene expression and the function of regulatory sequences like promoters or replication origins, thereby progression through the cell cycle [4].

The reconfiguration of local chromatin creates specialized domains. Accessibility of regulatory elements is facilitated by four processes that change chromatin structure. First, ATP-dependent chromatin remodeling complexes are able to slide, disrupt or remove nucleosomes [5]. Second, N-terminal tails of histones can be modified by addition of covalent modification(s) such as acetylation, methylation, ubiquitination, sumoylation and/or phosphorylation [6]. Third, histone chaperones participate in the regulated assembly and disassembly of nucleosomes during most DNA transactions [7]. Finally, the incorporation of non-canonical histone variants within nucleosomes leads to specialized chromatin domains [8]. Some histones have variants that differ in amino acid sequence from the canonical one and can be exchanged in the same nucleosome at specific locations in the genome. Specific incorporation of variants can be performed by specific ATP-dependent remodeling complexes and/or specialized histone chaperone [8–10].

2. Histone H2A.Z

Histone H2A has the largest number of variants with specific and highly conserved functions. Particular H2A variants like H2A.Z or H2A.X have important functions for cell proliferation and viability and are implicated in different processes [11]. The phylogenetic studies of histone variant H2A.Z showed an early divergence in evolution between species, acquiring specialized functions [12]. *H2A.Z* genes are essential for development and viability in many organisms. Disruption of *H2A.Z* genes leads to lethality in *Tetrahymena thermophila* [13], *Xenopus leavis* [14,15], *Drosophila melanogaster* [16,17] and

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mice [18,19]. In *Drosophila*, the lethality of H2A.Z (called H2Av) null can be rescued with the injection of H2A.Z in early larval stages suggesting an important role for H2A.Z in development [17]. In budding yeast, H2A.Z (Htz1) is not essential but leads to slow growth and defects in transcription activation of genes [20,21]. Since deletion of H2A.Z in yeast is non-lethal, it was used to map the genetic interaction network with other genes, leading to a better understanding of its functions. In parallel, genome-wide studies established its precise locations throughout the genome, which greatly helped to understand its role in chromatin structure and function [22–29]. Roles for H2A.Z have been reported in gene transcription [21], chromosome segregation [30], DNA repair [31], heterochromatin silencing [32–34], and progression through the different phases of the cell cycle [35].

Interestingly, while canonical histones are synthesized during S-phase, H2A.Z is constitutively expressed throughout the cell cycle [36]. Its incorporation in chromatin is replication-independent and at non-random locations [37]. The replacement of histone H2A with the H2A.Z variant is catalyzed by ATP-dependent chromatin remodeling complexes and plays an important role in maintaining chromosome integrity. Many groups have studied the regulation of H2A.Z deposition/eviction on chromatin. Important works on the particular structure of H2A.Z-containing nucleosome and on remodeling-complexes responsible for H2A.Z incorporation in chromatin generate a model for the regulation of H2A.Z deposition through crosstalk with other chromatin-modifying complexes. The focus of this review will be on the molecular mechanisms that direct the incorporation of H2A.Z in chromatin and the general regulation of deposition/eviction in eukaryotic cells.

3. H2A.Z-specialized local chromatin structure

Histone variants differ from the canonical ones in their primary sequences and by specific nucleosome properties within chromatin [38]. The addition of variants can change the physiochemical properties of the nucleosome (Fig. 1A). As a consequence both the stable interaction between DNA and nucleosome as well as the accessibility of the DNA can be altered [39]. H2A.Z variants share about 90% similarity among the various higher eukaryotes. H2A and H2A.Z differ in amino acid sequence but share about 60% of identity [40]. These changes are sufficient to create a unique chromatin structure in H2A.Z enriched regions. H2A.Z differs from H2A by a C-terminus containing an alternative docking domain and an extended specific acidic patch. Recent genetic studies identified H2A.Z residues in the acidic patch and C-terminal docking domain that are important for its deposition into chromatin [41,42]. This replacement creates a different interface in the nucleosome that can recruit specific factors/modulators (Fig. 1D). The specific configuration of the H2A.Z-containing nucleosome can facilitate nucleosome–nucleosome interactions within the chromatin, modulating higher-order chromatin structure near telomeres [43]. The crystal structure of H2A.Z-containing nucleosome illustrated the importance of the H2A replacement by H2A.Z [44]. This structure allowed authors to conclude that replacement of H2A by H2A.Z leads to major distortions and to suggest subtle destabilization of the octamer containing the variant.

Many biophysical studies have been done to understand the properties of H2A.Z-containing nucleosomes. Some studies observed a fragility [22,44–46] while others observed a stabilization when compared to canonical nucleosomes [43,47–49]. In purified yeast purified native chromatin, Zhang et al. showed that nucleosomal H2A.Z is more unstable and susceptible to loss upon salt increase compared to H3 or H2A [22]. Abbott et al. characterized by analytical centrifugation the ionic strength dependence of H2A.Z in reconstituted nucleosomes and conclude that this variant may play a chromatin-destabilizing role [45]. In contrast, Park et al. observed by fluorescence resonance energy transfer (FRET) assays that H2A.Z stabilizes the octamer compared in comparison to H2A [47]. Some biophysical techniques were also used to suggest that H2A.Z/H2B dimers are more loosely associated than H2A/H2B [46], while others indicate that H2A.Z facilitates the folding of the 30-nm chromatin fiber and heterochromatin formation [43,48]. To better understand the experimental procedures and limitations of these interesting studies, we refer the reader to a review by Hansen [50]. It is clear that these apparently contradicting data could be partially explained by the context in pre-existing higher order chromatin and/or post-translational modifications present on the nucleosomal histone tails. H2A.Z-containing nucleosomes possess unique biophysical properties that could be more stable or unstable depending on the pre-existing histone marks or the ones carried by H2A.Z itself (e.g. [23,49,51–53](see below). Another example of context-dependency is the combined effect of human H2A.Z and H3 variant H3.3 in the same nucleosomes, which are more unstable than nucleosomes containing only one of the two variants [54]. Accordingly, the incorporation of H2A.Z in H3.3-nucleosomes at specific loci in the genome is correlated with nucleosome-depleted regulatory regions [55]. Interestingly, H3.3 corresponds to the major H3 form in budding yeast, suggesting that incorporation of H2A.Z is sufficient to poise nucleosomes for destabilization while a higher level of regulation is present in human cells.

Furthermore, an H2A.Z-containing octamer could exist in two different states: with two copies of H2A.Z–H2B dimers, called homotypic state (ZZ), or with only one copy along with a canonical H2A–H2B dimer, called heterotypic state (AZ). Two recent studies confirmed that both ZZ and AZ forms exist in chromatin in vivo [56,57]. Luk et al. calculated the relative distribution of both nucleosome configurations and evaluated it at 35% and 65% respectively [56]. It is possible that the ZZ nucleosome structure may be more unstable than AZ or AA nucleosomes.

Thus, once incorporated into chromatin, H2A.Z provides different biophysical properties to the nucleosome, often linked to an open chromatin structure. Deposition needs to take place at specific regions to avoid distortion in chromatin at random locations and the first step of deposition is played by histone chaperones.

4. Deposition is assisted by specific histone chaperones

It is now believed that the majority of H2A.Z incorporation into chromatin is performed by Swr1-related ATP-dependent chromatin remodelers that specifically exchange canonical H2A–H2B for H2A.Z–H2B dimers within nucleosomes [58] (discussed in section below). It is also believed that specific chaperones are able to provide H2A.Z–H2B dimers to the exchange reaction or during chromatin assembly. Histone chaperones are known important modulators of chromatin organization [7]. Various chaperones have been described to interact with H2A.Z–H2B dimers in vivo (Fig. 1A) [59–61]. Nucleosome assembly protein 1 (Nap1) is a chaperone for canonical H2A–H2B dimers but has also been described to interact with unincorporated H2A.Z–H2B dimers [60,61]. Nap1 imports the variant histone dimer into the nucleus [62] and escorts it to the SWR1-related complexes responsible for its incorporation into chromatin [61]. In addition, the Chz1 protein has been found to be a specific chaperone for H2A.Z–H2B dimers [60]. Chz1 has been described to act in the nucleus in the transcriptional control of subtelomeric genes [63]. Finally, the FACT complex that has been implicated in H2A–H2B incorporation and eviction has also been proposed as a possible H2A.Z chaperone [59,60]. In the absence of Nap1 and Chz1, FACT is able to escort H2A.Z–H2B for dimer exchange by the SWR1 complex in vitro [60]. The relative importance of these different chaperones in H2A.Z deposition is not well understood in part because the in vitro exchange assay with SWR1 complexes does not require the presence of chaperones [61].

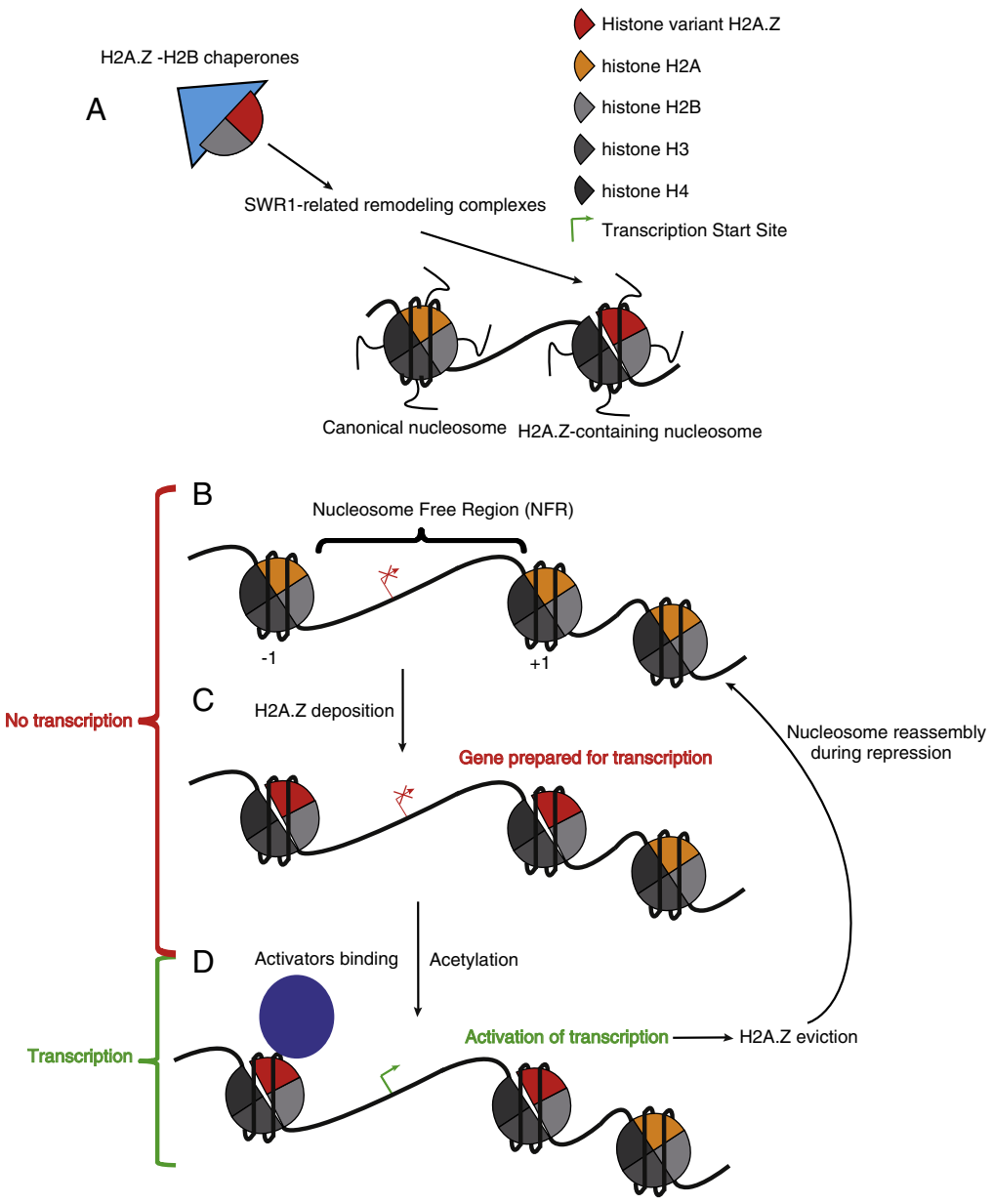

Fig. 1. Schematic representation of histone H2A.Z role in gene activation. (A) Incorporation of H2A.Z in chromatin by the replacement of H2A–H2B dimers with H2A.Z–H2B dimers. ATP-dependent exchange by Swr1-related complexes is assisted by H2A.Z–H2B chaperones. H2A.Z-containing nucleosomes are less stable than canonical nucleosomes. (B) Promoter of yeast inactive gene has a nucleosome-free region (NFR) surrounded by two well positioned nucleosomes. (C) Specific incorporation of H2A.Z at nucleosomes −1 and +1 poises genes for transcriptional activation. (D) Binding of activators leads to H2A.Z acetylation, eviction of H2A.Z nucleosomes and transcription initiation.

5. Deposition occurs at specific locations in the genome

The focus of this review is the mechanism of H2A.Z deposition/eviction in chromatin, but to understand how deposition occurs we need to understand where it happens. Because the canonical histone octamer occurs approximately every 200 bp over billions of DNA base pairs in the genome, non-random H2A.Z deposition on chromatin must be very specific and highly regulated.

Different genome-wide chomatin immunoprecipitation (ChIP) studies in several organisms precisely mapped H2A.Z along chromosomes. In yeast, H2A.Z is distributed mostly at RNA polymerase II promoters, both active and inactive, at two specific nucleosomes, one upstream and one downstream of the transcription start site (nucleosomes −1 and +1 compared to TSS) (Fig. 1B and C) [22,24,29,64]. Its localization is flanking the nucleosome free region (NFR) and is important for the regulation of gene transcription (Fig. 1C). In higher eukaryotes, the same enrichment has been observed around the TSS [25] but seems to be mostly at active genes [28,55,65–67]. H2A.Z occupancy is preferentially located on gene regulatory regions like promoters, insulators and enhancers suggesting a role in the regulation of gene expression [25,68].

As mentioned before, H2A.Z-containing nucleosomes can exist as either the AZ or ZZ form. Because ChIP analysis cannot easily distinguish these two forms, their presence was alternatively determined both in vitro and in vivo. Both forms can be detected through in vitro nucleosome reconstitution [44,69]. Interestingly, Luk et al. observed that both heterotypic and homotypic H2A.Z nucleosomes are similarly enriched at promoters of genes in yeast [56]. However, another team found that in *Drosophila* only homotypic H2A.Z nucleosomes are present in active promoters of genes [57].

The fact that H2A.Z is enriched in the promoter of inactive genes in yeast lead to the hypothesis that it may help the activation process by poising the chromatin structure [22,24,29,70,71].

6. Roles at multiple steps of transcription

The transcriptional role of H2A.Z was first observed by Allis and colleagues who found this variant in the transcriptionally active macronucleus of *Tetrahymena thermophila* [72]. Since then, contradicting data have been found in different organisms suggesting a positive or a negative role in transcription. In yeast, the non-lethal Δ*htz1* strain showed a defect in the activation of inducible genes confirming a positive role in transcription [21,35,71,73]. It was shown that H2A.Z has important functions during transcription initiation [71].

In yeast, it is also now known that H2A.Z is found at the promoter of inactive or less transcribed genes and tends to be lost after activation of these genes (Fig. 1D). On the other hand, only 109 genes are upregulated in a Δ*Htz1* mutant strain [32]. H2A.Z enrichment is inversely correlated with transcription of genes in yeast [22–24,70], but the opposite is found in human and *Drosophila* cells, where H2A.Z enrichment at promoters correlates with the level of gene expression [25,27]. While H2A.Z is preferentially located at the promoters of active genes in higher eukaryotes, it still also tends to be lost from promoters after transcription activation. It has been suggested yeast H2A.Z-containing nucleosomes prepare genes for their activation because they are more easily disassembled than canonical nucleosomes, through the fragility of their structure (Fig. 1C) [22,24].

There is a general positive correlation between the levels of H2A.Z and RNA polII in at promoters in human cells [67]. This suggested that H2A.Z helps to recruit the transcriptional machinery by changing the local chromatin structure organization of the nucleosome at poised promoters and by the recruitment of transcriptional activators leading to the stimulation of transcription (Fig. 1D) [20,67,74,75]. Then, genomewide mapping experiments in *Drosophila* showed a regulation in composition of transcription elongation factors on H2A.Z nucleosomes suggesting an additional role in transcription elongation [57]. A recent study clearly demonstrates genetic interactions with genes encoding transcription elongation factors, strongly suggests a positive role for H2A.Z during elongation [76].

H2A.Z has also been described to confer transcriptional memory through its relocalization from the nucleoplasm to the nuclear periphery upon activation [77]. In yeast, epigenetic transcriptional memory has been linked to increased H2A.Z deposition at the promoters of inducible genes [77–80]. On the other hand, a direct role in transcription memory has been debated [79,81,82] and such function has not been demonstrated in higher eukaryotes. It is important to point out that, in yeast Δ*htz1* strains, many phenotypes could be due to inappropriate actions of the actors controlling H2A.Z incorporation, e.g. SWR1/INO80. The suppression of an *htz1* mutant phenotype by *SWR1* disruption suggests that the SWR1 complex does damaging things to chromatin when H2A.Z is not available for deposition/exchange [79,83] (see below).

7. Important roles for H2A.Z to maintain genome integrity

The fact that the deletion of the H2A.Z gene is lethal in most eukaryotes may be indicative of its many roles in the cell. Currently, its various functions in transcription are most well characterized. However, thanks to loss of function studies, it has been proposed that H2A.Z variants play roles in other cell processes important for genome maintenance and integrity [84].

H2A.Z is implicated in chromosome integrity through functional interactions with factors required for proper chromosome segregation and cytokinesis [30,85–87]. A *Δhtz1* strain leads to chromosome loss and genetically interacts with microtubule components. In fission yeast, the putative demethylase Msc1 interacts with the SWR1 remodeling complex through its PHD domains and inhibits H2A.Z incorporation at centromeres (Fig. 2A) [88,89]. This variant is also linked to

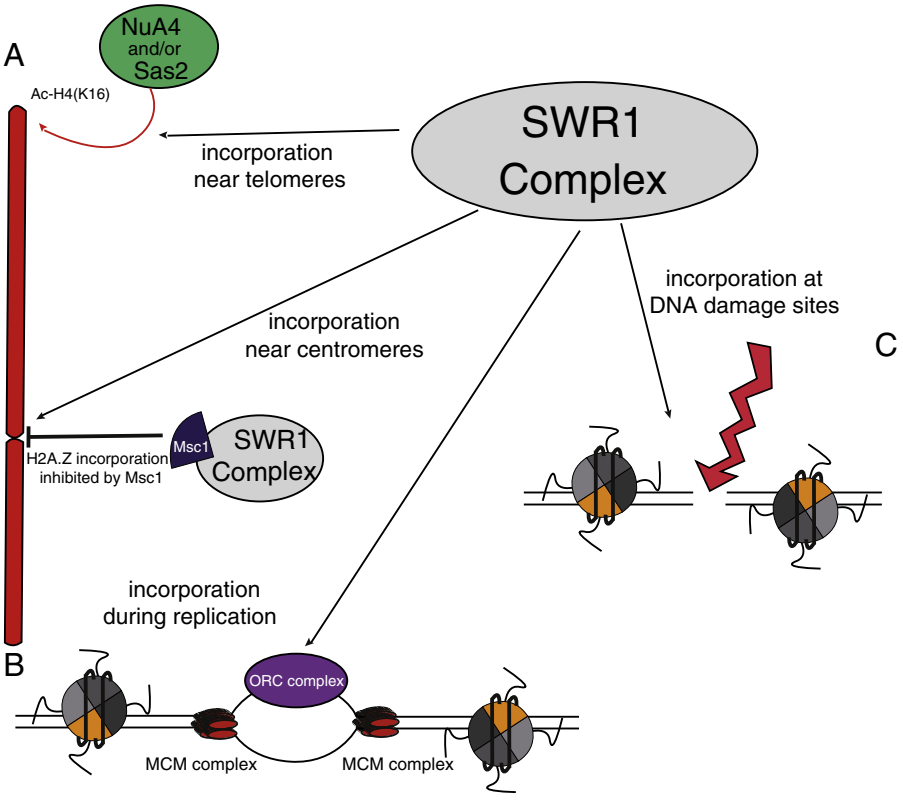

Fig. 2. Incorporation of H2A.Z by SWR1 in different nuclear processes linked to genome stability. (A) Centromere and telomere integrity depends on adjacent incorporation of H2A.Z by SWR1. Incorporation directly at centromeres is inhibited by Jumanji protein Msc1. H2A.Z deposition near telomeres is stimulated by Sas2 acetyltransferase activity on H4K16 as well as by the NuA4 complex. (B) Emerging role of H2A.Z in firing of replication origins and S-phase progression. (C) Role for H2A.Z in DNA damage repair pathway. H2A.Z is transiently mapped at DNA double-strand breaks in a role linked to persistent damage.

chromatin boundaries as it prevents the spreading of heterochromatin [32,51,90] besides being involved in the integrity of centromeres [30,86,91,92] and telomeres [93,94] (Fig. 2A).

Dhillon et al. proposed a role for H2A.Z in cell cycle progression since Δ*htz1* mutant strains show a delay in S phase progression and in the firing of replication origins [35,95]. A large-scale study showed physical interaction between H2A.Z and the replication protein ORC1 and genetic interactions with other replication factors like ORC1, ORC5 and PCNA, supporting a role in replication [35]. In agreement with such a role, H2A.Z has been found to colocalize with replication origins in *Arabidopsis thaliana* [96]. In addition, Δ*htz1* cells have been shown to be sensitive to DNA damage agents during DNA replication [61,97]. Moreover, H2A.Z is required for S-phase checkpoint activation since it regulates cyclin genes. Thus, it appears that H2A.Z is implicated in the DNA damage response checkpoint upon replicative stress (Fig. 2B).

Recently, a role for H2A.Z in DNA repair has emerged. H2A variants, mainly H2A.X, play a major role in DNA repair signaling [98]. Kalocsay et al. have transiently mapped sumoylated-H2A.Z at DNA double strand breaks (DSBs) [31]. Deposition seems to occur rapidly after induction of breakage, suggesting an early role of H2A.Z during DNA repair (Fig. 2C). Moreover, Δ*htz1* cells are sensitive to many DSB-inducing agents and display defects in DNA resection [31]. Interestingly, sensitivity to drugs like MMS is suppressed by disruption of the *HDA1* gene, which encodes a major histone deacetylase [99,100]. It remains to be determined if this process is conserved in higher eukaryotes. Another interesting observation is that mutating SWR1 subunits in a Δ*htz1* background reverses the strong sensitivity to hydroxyurea, suggesting again that, in the absence of H2A.Z, the SWR1 complex does abnormal things to chromatin leading to specific genome stability defects [79,83,99](see below).

8. Conserved chromatin-remodeling complexes act in H2A.Z deposition/eviction

All these different roles of H2A.Z variant implicate recruitment mechanisms for deposition at specific loci. Incorporation in chromatin implies different steps. To replace canonical dimers by variant dimers, SWR1-related complexes evict them from the nucleosome and replace them by H2A.Z-containing dimers. But the opposite is also required in order to reset the nucleosome, i.e. H2A.Z needs to be removed and exchanged for canonical histone H2A. It has been proposed that this process of deposition/eviction is catalyzed by two families of large ATP-dependent complexes, both highly conserved during evolution.

The alteration of histone–DNA interactions is made by large ATP-dependent chromatin-remodeling enzymes complexes. Using the energy from ATP hydrolysis these complexes are able to slide, disrupt, evict nucleosomes or exchange histone-dimers [5]. A subclass of the SWI2/SNF2 superfamily of enzymes is responsible for H2A.Z incorporation in chromatin [58].

Studies in yeast discovered an enzymatic complex responsible for most H2A.Z incorporation in vivo and for the specific replacement of H2A with H2A.Z in chromatin in vitro, but not the reverse reaction [61,97,101]. This complex, called SWR1, specifically removes H2A–H2B dimers from the nucleosome and replaces them with H2A.Z–H2B dimers [61]. This action requires the SWI2/SNF2 ATPase/helicase domain of the Swr1 subunit (Fig. 3A).

The purification of yeast SWR1 complex revealed that it is comprised of 14 subunits (Fig. 3A) including the ATPase subunit Swr1 as well as the other non-essential gene products Bdf1, Arp6, Yaf9, Swc2, Swc3, Swc5, Swc6 and Swc7. The complex also contains five essential gene products: Rvb1, Rvb2, Arp4, Swc4 (also called Eaf2) and Act1. Some subunits have functions apart from SWR1

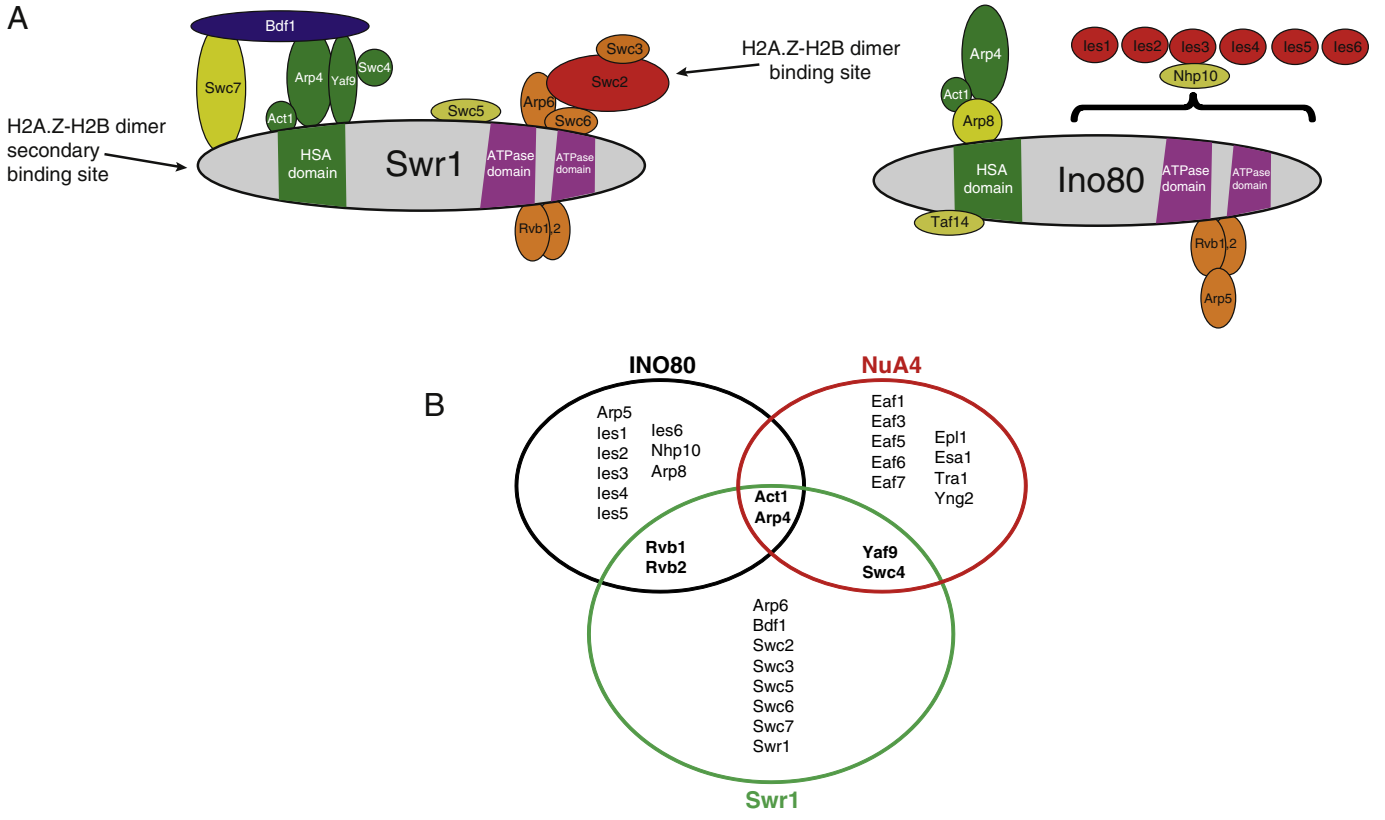

Fig. 3. Composition of yeast ATP-remodeling complexes that regulate H2A.Z deposition. (A) Composition of the SWR1 and INO80 complexes and their known interactions. (B) Subunits shared by ATP-remodeling complexes INO80 and SWR1 with the NuA4 histone acetyltransferase.

and are shared between other important chromatin-regulating complexes such as NuA4 and/or INO80, suggesting a functional link between these complexes (Fig. 3B) [102–105].

More recently, different studies in higher eukaryotes identified p400 and SRCAP (SWI2/SNF2-related CBP activator protein) complexes as homologous to the SWR1 complex. Each of these harbors histone replacement function both in vivo and in vitro (Fig. 4) [106–111]. The purification of these complexes showed functional conservation, as they were able to catalyze exchange activity similar to the yeast SWR1 complex [106–109]. These different complexes may be involved in different types of H2A.Z exchange depending on cellular stimuli and chromatin context.

In higher eukaryotes, the p400 protein is found associated with Tip60, a MYST-family acetyltransferase [112], creating a physical merge of the yeast SWR1 remodeler and NuA4 acetyltransferase complexes (Fig. 4) [104,113]. *Drosophila* Tip60 is able to acetylate chromatin and to exchange H2A.Z, demonstrating a close functional conservation of the fusion [109]. *Drosophila* H2A.Z is in fact a hybrid between H2A.X and H2A.Z and encompasses the activities of both variants [16]. *Drosophila melanogaster* Tip60 complex also has a p400/domino subunit homologous to Swr1 [114]. In human cells, p400 is implicated in the p53/p21 senescence pathway by inhibiting p21 and stimulating p53 toward apoptosis [115–117]. This complex is involved in H2A.Z exchange and responsible for incorporation of H2A.Z at specific promoters in vivo [108,118].

As described before, the destabilization of H2A.Z-containing nucleosomes seems to facilitate transcriptional initiation. H2A.Z eviction from a nucleosome is a rapid event, and as such little is known about this process. Recent studies searched for a specific activity responsible for the replacement of H2A.Z–H2B dimers by H2A–H2B [56,119]. Papamichos-Chronakis et al. found that the INO80 remodeling-complex promotes the eviction of H2A.Z from an in vitro exchange assay in an ATP-dependent manner [119]. Furthermore, they found that H2A.Z is evicted by INO80 in vivo after transcriptional induction. Ino80 is a chromatin-remodeling enzyme belonging to the same SWI2/SNF2 subfamily as Swr1 and plays a role in transcription, DNA repair and replication [58,120]. Under stress conditions the INO80 complex seems to be targeted to coding regions for elongation of transcription as well as replication forks [121–123]. H2A.Z eviction by INO80 in yeast suggests a role for this complex in the relocalization of H2A.Z in stress conditions (see below). It remains to be determined if the described mammalian INO80 complex plays similar roles in higher eukaryotes (reviewed in [124]).

It could be interesting to evaluate the various specific roles for these different complexes mediating H2A.Z exchange. The precise mechanism of how H2A.Z remodeling complexes deposit this variant is not well understood. However, different biochemical studies have shed some insight on this energy-consuming process.

9. Work shared by all subunits

Yeast SWR1 complex is a large complex of numerous subunits, each containing specific domain(s) which contribute to the overall structure of the complex or directly to the deposition activity. The recruitment of the complex to promoters is directly dependent on the protein/domain composition of SWR1 and is typically enriched to the same degree as H2A.Z [105,125]. Biochemical studies helped to characterize the role of each subunit. H2A.Z binds the SWR1 complex at two different locations on the N-terminal region of Swc2 (YL-1 in human p400 complex) and to a smaller extent to the N-terminal domain of Swr1 (Fig. 3A) [126,127]. The binding of H2A.Z–H2B dimer in SWR1 is assisted by specific chaperones (see above) (Fig. 1A).

The Swr1 subunit, which shares significant homology to the Eaf1 subunit of the NuA4 complex [104], is essential for H2A.Z incorporation in chromatin since it also contains the ATPase domain homologous to Swi2/Snf2 [9,58,102]. The K727G substitution on the ATP-binding pocket of Swr1 abrogates ATPase activity without affecting the composition of SWR1 complex [61]. This activity is strongly activated by H2A-containing nucleosome (AA or AZ forms independently) and this hyperstimulation is not found in the ATPase null-mutant [56]. These results indicate that ATPase activity of the Swr1 subunit is a key element for the SWR1 complex activity. In addition, Swr1 has an HSA domain (Helicase SANT-associated) which acts as a platform for the assembly of the complex (Fig. 3A) [126,128].

The Swc2/YL-1 subunit interacts directly with the C-terminus of H2A.Z and is essential for its transfer into chromatin [127]. Moreover, Swc2 associates with the ATPase domain of Swr1, an interaction that also requires the Swc6 and Arp6 subunits [126]. Moreover, in Δ*swc2* strains the amount of SWR1 complex on chromatin seems to be lower, suggesting that Swc2 is involved in SWR1 recruitment [83]. Deletion of Arp6 leads to an inactive SWR1 complex suggesting a role in Swr1 function. A recent paper showed that deletion of Arp6 in *Arabidopsis thaliana* grown at 17 °C has a pattern of gene expression similar to normal plants grown at 27 °C suggesting a role in the transcriptional response to temperature variation [129].

The Yaf9 subunit (GAS41/YEATS4 in humans) is shared between SWR1 and NuA4 complexes and has a YEATS domain able to bind histones H3 and H4 in vitro [130]. H2A.Z incorporation is crippled in the absence of Yaf9 and this is dependent on its YEATS domain [130]. Moreover, the Swc5 subunit has recently been implicated in histone replacement in vivo [83].

The Arp4 subunit plays a key structural role in SWR1 complex integrity. It is required for H2A.Z incorporation in vivo and in vitro and for the association of Bdf1, Yaf9, Swc4 and Act1 [126]. The tetrameric subcomplex comprised of Arp4-Yaf9-Swc4-Act1 exists in both SWR1 and in NuA4 (Fig. 3B). This sharing could mediate the cooperation between these two complexes [9,102,105]. This tetrameric subcomplex allows association of the Bdf1 subunit with SWR1 but intriguingly not with NuA4 [130].

Bdf1 (Bromodomain Factor 1) is an interesting protein, homologous to Brd8 in p400 complexes. Bdf1 is largely implicated in transcription via its interaction with TFIID subunit during RNA polII initiation [125,131]. This protein contains two bromodomains that can associate with acetylated H4 tails both in vitro and in vivo [132,133]. Moreover, Bdf1 functionally interacts with Esa1, the only essential enzyme responsible for H4 and H2A histone tail acetylation in yeast [125,133,134]. Deletion of Bdf1 or acetylated histone tails leads to defects in H2A.Z incorporation at promoters, suggesting a crosstalk through this bromodomain protein during H2A.Z deposition on chromatin [22,29,125,135].

10. Post-translational modifications implicated in deposition

Post-translational modifications of histone tails are involved in the alteration of higher-order folding of chromatin and in the creation of binding sites for non-histone proteins [136]. Acetylation of lysine residues by acetyltransferases represents a major post-translational modification which occurs in the cell on either histones or non-histone proteins [137].

The N-terminal tail of H2A.Z is acetylated in different species [68,138–141]. Human H2A.Z is precisely acetylated at residues K4, K7, K11 and K13 while yeast H2A.Z is acetylated at K3, K8, K10 and K14 residues (Fig. 5A) [29,79,117]. This acetylation is dependent on the Gcn5 and Esa1 acetyltransferases [23,51,52,139]. H2A.Z K14 is the predominant residue found acetylated in yeast [23]. It colocalizes on promoters of active genes as well as on ORFs. Its localization on theses coding regions positively correlates with level of transcription, confirming the role of acetylated H2A.Z during transcription [23,68,79]. In absence of H4 acetylation, acetylation of H2A.Z is required to block heterochromatin spreading [51,139]. Surprisingly, the mutation of K14R residue displays selective sensitivity to benomyl, a drug used to detect kinetochore and spindle checkpoint

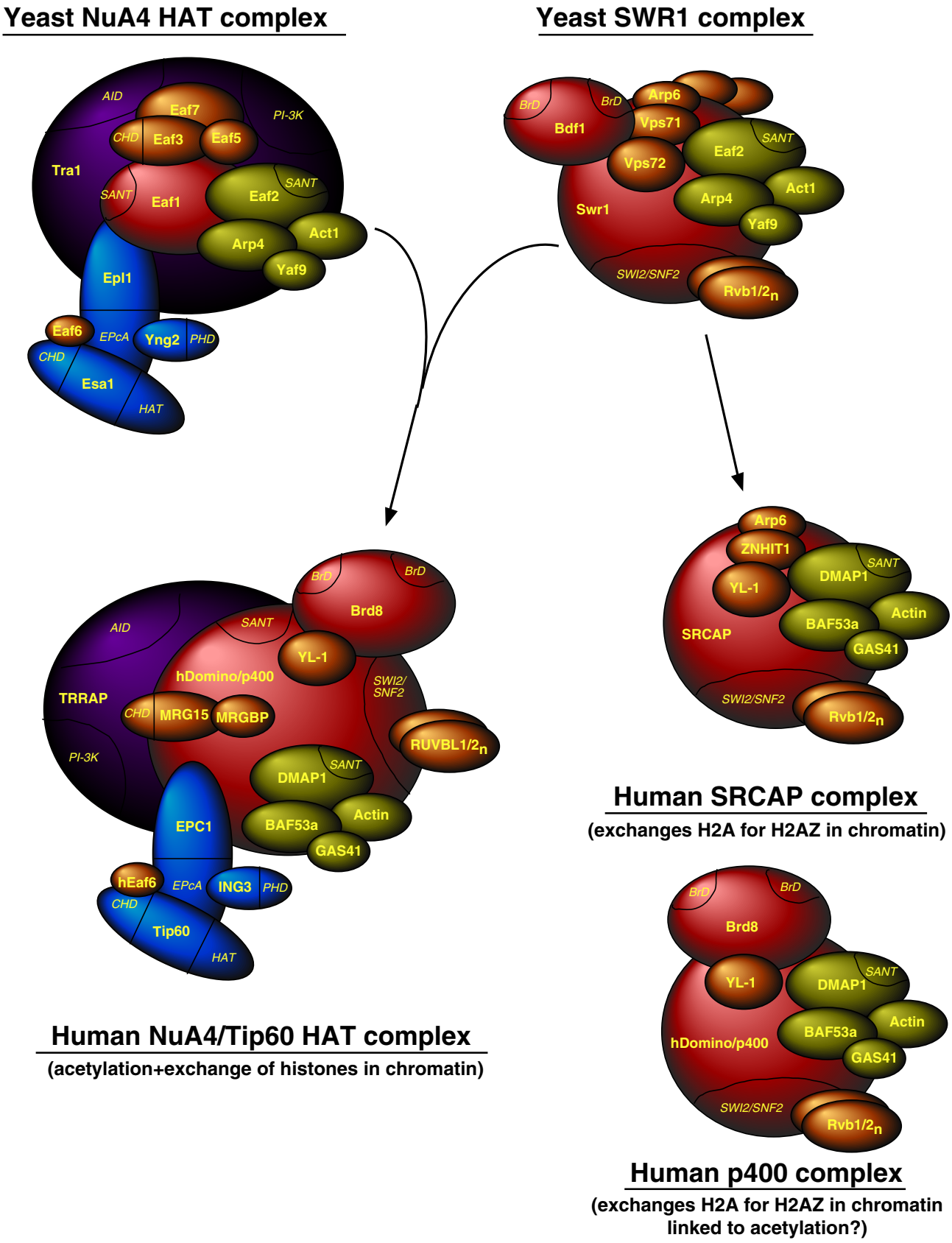

Fig. 4. SWR1-related complexes in mammalian cells. Note: The full subunit composition of a p400 complex independent of the Tip60–p400 is partly speculative based on the literature and our unpublished data.

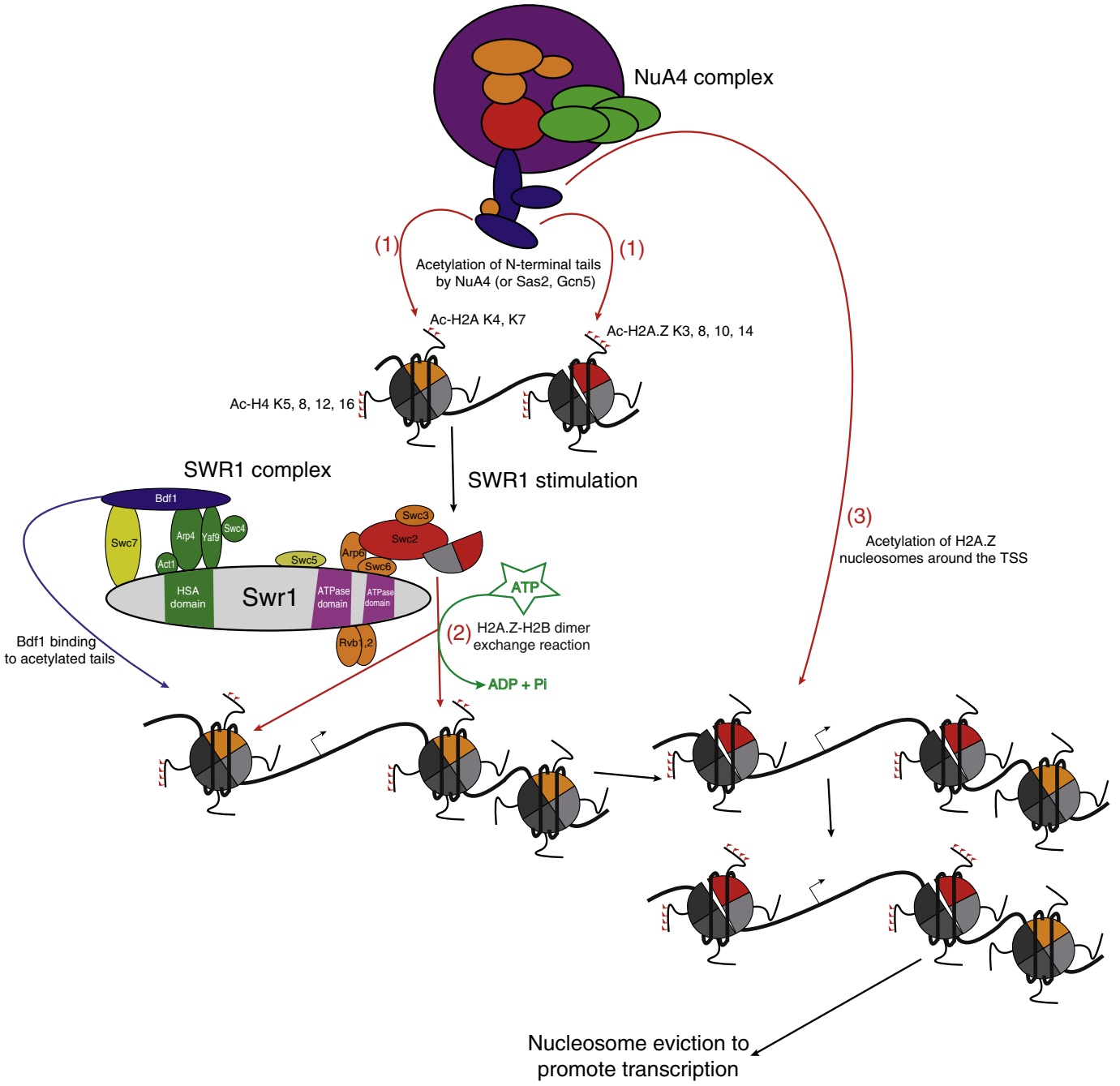

Fig. 5. Schematic representation of H2A.Z deposition by the SWR1 complex and the connection with histone acetylation. (1) Canonical H2A, H4 and variant H2A.Z histones are acetylated by yeast NuA4 acetyltransferase. (2) Acetylation of H2A and H4 N-terminal tails by NuA4 stimulates the SWR1 complex through interaction with its bromodomain subunit Bdf1. This leads to enhanced ATP-dependent dimer exchange activity which replaces H2A–H2B dimers with H2A.Z–H2B dimers. (3) NuA4 acetylates H2A.Z N-terminal tails to promote local chromatin remodeling and gene activation.

mutants. Moreover, this mutant shows an increase in the rate of chromosome loss [52,138]. Importantly, H2A.Z acetylation occurs in vivo at promoters only after its incorporation into chromatin, implying that it has no role in H2A.Z deposition [51,52].

A functional link between acetyltransferase activity, ATP-dependent chromatin remodeling and H2A.Z had previously been described in yeast arguing for redundancy between Gcn5, Swi2 and Htz1 [21]. Interestingly, the NuA4 histone acetyltransferase complex shares 4 subunits with the SWR1 complex and functionally cooperates with it (Fig. 3B) [105,125,135]. NuA4 acetylates H4 and H2A N-terminal tails of canonical nucleosomes at promoters of genes, which stimulates SWR1 activity and H2A.Z incorporation (Fig. 5B) [135]. Both the human and *Drosophila* Tip60/p400 acetyltransferase complexes contain subunits homologous to the yeast SWR1 complex and are also able to target, exchange and modify H2A.Z [104,108–110]. These data support the hypothesis that there is a connection between acetylation and histone exchange activity. This cooperation helps to preset the chromatin structure of highly inducible genes [142]. The Bdf1 subunit which is not required for the exchange reaction has a role in SWR1 recruitment to acetylated chromatin (Fig. 6C) [125,135]. Another link between H4 acetylation and H2A.Z deposition has been found with the Sas2 histone acetyltransferase which is able to play a role in deposition through acetylation of H4K16. This seems to promote H2A.Z deposition specifically at subtelomeric regions (Fig. 2A) [93,94,143,144].

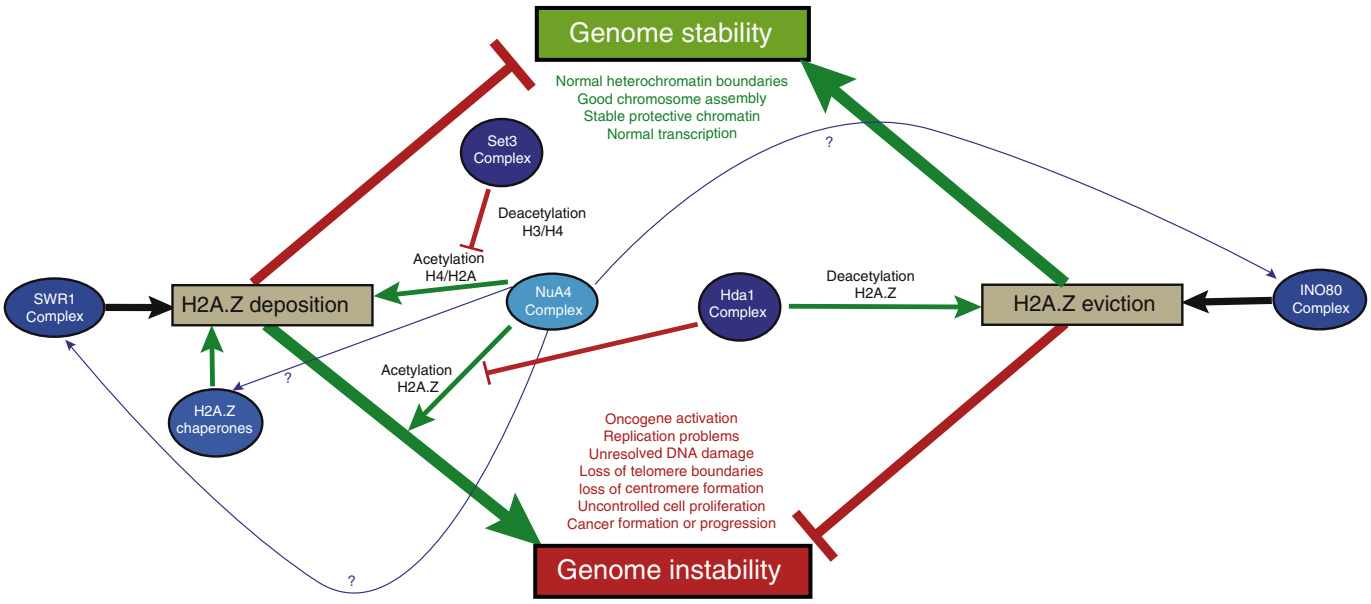

Fig. 6. Implication of the different steps of H2A.Z deposition/eviction in genome stability.

In a recent paper, Papamichos-Chronakis et al. showed that INO80 is able to exchange unacetylated form of H2A.Z for H2A in vitro [119]. They observed that in a Δ*ino80* strain only unacetylated H2A.Z is mislocalized. These data suggest that mislocalized-unacetylated H2A.Z destabilizes the genome (Fig. 6).

Acetylation is a reversible modification and H2A.Z-deacetylation is regulated by Hda1. The *Δhda1* strain leads to an increase in H2A.Z acetylation [100,119]. An interesting possibility would be to see if Hda1 is recruited to specific regions to deacetylate H2A.Z in order to favor H2A-containing nucleosomes through INO80 action (Fig. 6).

A recent study looked at a combination of synthetic growth defect mutants and revealed a possible new player in this histone exchange pathway [99]. Set3 is a component of HDAC3 complex which is responsible for H3 and H4 deacetylation [145,146]. It is recruited to the 5′ end of actively transcribed genes via the Set3 PHD domain which binds H3K4me3 [146]. The new study shows that the triple mutant Δ*htz1* Δ*swr1* Δ*set3* reverses the slow growth phenotype in comparison to the separate double mutants Δ*htz1* Δ*set3* and Δ*swr1* Δ*set3* [99]. This suggests that the Set3 histone deacetylase complex could participate in H2A.Z-deposition and function, and again indicates that SWR1 activity is detrimental in absence of H2A.Z. In the same study, a close functional link between SWR1 activity and the SAGA H2B deubiquitination subcomplex has also been found, in agreement with a previous link established between Chz1 and H2B ubiquitination [63].

Another interesting avenue of study will be to elucidate the molecular mechanism of H2A.Z function in DNA damage response. SWR1, INO80 and NuA4 complexes all share the Arp4 subunit, which has been implicated in their binding to sites of double strand breaks via interaction with phosphorylated-H2A, the yeast homolog of mammalian γ-H2A.X [103]. These complexes play a key role in the DNA damage response pathway, so it is interesting to study the close cooperation between these complexes in this process [121,147,148].

A recent study reported NuA4 activity for non-histone substrates [149]. Among these are subunits of ATP-dependent chromatin remodeling complexes like Ies2, an INO80 subunit, and Bdf2, a protein redundant with Bdf1 [58,125,131]. Another interesting result is that H2A.Z chaperones Nap1, Chz1 and Spt16 or other histone chaperones like Vps75 have been found to be acetylated by NuA4 in vitro [149]. This suggests a possible feedback control of the available H2A.Z pool by NuA4 (Fig. 6).

In addition to acetylation, H2A.Z is subject to other posttranslational modifications such as ubiquitylation and sumoylation [31,150,151]. Yeast sumoylated-H2A.Z at K126 and K133 plays a role in DNA damage response by participating in the relocalization of the double strand break to the nuclear periphery [31]. It will certainly be interesting to study if human sumoylated-H2A.Z plays a role in the cellular response to DNA damage.

11. Eviction to maintain genome integrity

Maintaining stability and integrity of the genome is essential for cell survival. As such, genomic instability is a common hallmark of many human cancers [152]. The regulation of chromatin structure is an important player in the maintenance of genome integrity. As we have already discussed in this review, H2A.Z has diverse important roles such as transcription, chromatin boundaries and at certain regulatory elements. As a result, expression itself has to be highly controlled because overexpression is linked to uncontrolled cell proliferation whereas downregulation results in genome instability [84,153]. Surely, the regulation of its localization is an essential way to prevent genome instability [83,119]. This regulation is mainly performed by interplay between chromatin-remodeling complexes SWR1 and INO80, and the action of other chromatin factors like acetyltransferases.

Strains which cannot form a SWR1 complex, that have an inactive SWR1 complex, or are deleted for the Ino80 subunit all showed a high sensitivity to various drugs due to the mislocalization of H2A.Z [83,119]. This important data suggests that SWR1 and INO80 complexes are responsible for the specific H2A.Z localization in chromatin and thus, are responsible for the proper control of H2A.Z-deposition/eviction. These results indicate that mislocalized H2A.Z has an impact on the genome stability (Fig. 6).

To preserve the stability of the genome, INO80 function seems to be a central key in stress conditions, and for example in H2A.Z localization [119,154]. We can hypothesize that the special structure adopted by H2A.Z-containing nucleosome could create new chromatin domains where H2A.Z should not be present. This reorganization in the genome causes transcription misregulation and directly affects the expression of genes regulated by normal H2A.Z deposition. In the context of an aberrant H2A.Z deposition, gene expression is likely affected. In fact, H2A.Z regulates the transcription of several important tumor suppressor or oncogenes like c-myc, BRCA1 or p21 by

presetting chromatin structure at promoters of the gene [25,66]. For example, when damage occurs, p21 expression requires H2A.Z eviction to allow p53 binding to the promoter and activated transcription [108]. H2A.Z modulates expression of both oncogenes and tumor suppressors that result in a stimulation of cancer cell proliferation [153,155–157].

Moreover, the regulation of the acetylation state of H2A.Z seems to have an essential role for its localization and in cellular process because mislocalized H2A.Z-containing nucleosomes are unacetylated while those found at promoters are acetylated [119]. In *Tetrahymena thermophila* non-acetylable H2A.Z lysines result in the death of the organism [140]. In yeast, unacetylable-H2A.Z is not sensitive to DNA damage [23,119]. However, unacetylable-H2A.Z in the absence of INO80 function is very sensitive to DNA damage and replicative stress. This suggests that acetylation of H2A.Z is not responsible for genome integrity but that it is essential for INO80 function to maintain genome integrity [119]. A recent study in cancer cells showed that H2A.Z acetylation is a key modification associated with gene deregulation in cancer [158].

12. Perspectives

H2A.Z is closely linked to genome integrity and cancer. In fact, problems in H2A.Z expression level are found in cancer cell lines where its overexpression is linked to disease progression [153,159–161]. Moreover, altered H2A.Z functions lead to tumorigenesis notably for progression to the metastatic stage and now represent a possible new target for cancer therapies [156,162]. In addition, this could be linked to its mislocalization due to an abnormal deposition leading to genome instability. A major role for H2A.Z is to allow recruitment of factors that could be targeted for therapy. For example, *Drosophila* H2Av, which is a chimera of both H2A.Z and H2A.X, has been linked to the recruitment of PARP-1 [163]. PARP-1 seems to mediate changes in chromatin and stimulate transcription through the H2A variant. H2A.Z and PARP-1 are functionally connected since they are implicated in the same cellular defects [164,165]. Since PARP-1 is already a popular target in cancer therapy, it would be interesting to test/target the H2A.Z deposition pathway for the induction of genome instability in cancer cells.

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