H2A.Z and chromatin remodelling complexes: a focus on fungi

Zhenhui Chen, Nadia Ponts

CRITICAL REVIEWS IN MICROBIOLOGY
2020, VOL. 46, NO. 3, 321–337
https://doi.org/10.1080/1040841X.2020.1781784

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

H2A.Z and chromatin remodelling complexes: a focus on fungi

Zhenhui Chen and Nadia Ponts

INRAE, MycSA, Villenave d'Ornon, France

ABSTRACT

Chromatin is a highly dynamic structure that closely relates with gene expression in eukaryotes. ATP-dependent chromatin remodelling, histone post-translational modification and DNA methylation are the main ways that mediate such plasticity. The histone variant H2A.Z is frequently encountered in eukaryotes, and can be deposited or removed from nucleosomes by chromatin remodelling complex SWR1 or INO80, respectively, leading to altered chromatin state. H2A.Z has been found to be involved in a diverse range of biological processes, including genome stability, DNA repair and transcriptional regulation. Due to their formidable production of secondary metabolites, filamentous fungi play outstanding roles in pharmaceutical production, food safety and agriculture. During the last few years, chromatin structural changes were proven to be a key factor associated with secondary metabolism in fungi. However, studies on the function of H2A.Z are scarce. Here, we summarize current knowledge of H2A.Z functions with a focus on filamentous fungi. We propose that H2A.Z is a potential target involved in the regulation of secondary metabolite biosynthesis by fungi.

ARTICLE HISTORY
Received 18 October 2019
Revised 3 June 2020
Accepted 4 June 2020
Published online 25 June 2020

KEYWORDS
Chromatin; secondary metabolism; mycotoxins

Introduction

Fungi are a kingdom regrouping extremely diverse eukaryotes ("Stop Neglecting Fungi" 2017). It is estimated that there are 2.2–3.8 million fungal species on earth with a diversity of structures (Hawksworth and Lücking 2017). Among them, filamentous fungi, which are composed of a web of filaments called "hyphae", are often overlooked. Many of them are of considerable interest in biotechnology; they can be used as "living factories" to produce proteins and metabolites of interest (Wösten 2019), serve as decontamination agents of pollutants (Prigione et al. 2018), or as biocontrol agents (Benítez et al. 2004; Zhao et al. 2016; Sarrocco et al. 2019), for example. They are also potent producers of heterogeneous secondary metabolites (SMs), many of them with beneficial properties such as antibiotic compounds (Alberti et al. 2017). Nonetheless, many fungal SMs can also be harmful, as in the case of mycotoxins which are known as food spoilers resulting in reduced yields and deteriorated grain quality, such as aflatoxins (e.g. aflatoxin B1; AFB1), fumonisins, zearalenone (ZEN), type B trichothecenes (e.g. deoxynivalenol, or DON), type A trichothecenes (e.g. T-2 toxin), and ochratoxin A (OTA) (Hussein and Brasel 2001; Alberti et al. 2017; Gruber-Dorninger et al. 2019). Many of them are produced by *Fusarium* species, which are regarded as the most important fungal pathogens of plants and animals (Goswami and Kistler 2004). The production of SMs in filamentous fungi are regulated by various factors, including nutrient source, pH, or light for example (Caracuel et al. 2003; Katoh et al. 2007; Wong et al. 2008; Tisch and Schmoll 2010). More recently, chromatin structure changes were proposed to play a key role in the regulation of SM biosynthesis (see Pfannenstiel and Keller (2019) and Strauss and Reyes-Dominguez (2011) for reviews).

Inside the nucleus of fungal (and most eukaryotic) cells, genomic DNA is packaged with histones to form nucleosomes, which are the basic unit of chromatin. Each nucleosome consists of two copies of each of the four core canonical histones H2A, H2B, H3 and H4, with ~150 base pairs (bp) of DNA wrapped around them (Richmond et al. 1984; Luger et al. 2012). These canonical histones are highly conserved across eukaryotic species and represent the major part of the total histone pool within an organism (Mariño-Ramírez et al. 2005). In most eukaryotes, each of these canonical histones is encoded by multiple genes with high sequence similarity and deposited into chromatin only during the S phase of the cell cycle after DNA replication (Talbert

CONTACT Nadia Ponts nadia.ponts@inrae.fr INRAE, MycSA, Villenave d'Ornon, France
Supplemental data for this article can be accessed here.

and Henikoff 2014). In metazoans, histone mRNAs are devoid of introns and are not polyadenylated. Instead, they have special stem-loop structures to trigger translation (Marzluff and Koreski 2017). In yeast, histone mRNAs are polyadenylated, polyA tail lengths varying during cell cycle (Beggs et al. 2012). They are expressed exclusively at the late G1 and S phase, i.e. when DNA replication occurs (Kurat et al. 2014). Whilst histone genes are also largely devoid of introns, with few exceptions such as one H4 gene in *Yarrowia lipolytica*, Basidiomycota and Ascomycota have introns in their histone genes (May and Morris 1987; Nishida and Yun 2011). In *Aspergillus nidulans*, expression of histones was shown to be also cell cycle-regulated (Ehinger et al. 1990). At the protein level, N-terminal tails of histones are extensively marked by covalent post-translational modifications (or PTM) including methylation, phosphorylation, acetylation, or ubiquitylation, that impact gene expression by altering chromatin state (Marzluff and Koreski 2017).

Additional non-allelic isoforms of canonical histones, called histone variants, also exist in all eukaryotes (Talbert and Henikoff 2010, 2014, 2017). In contrast to canonical histones, most of them are encoded by a single gene containing one or more introns expressed throughout the cell cycle, and can thus be incorporated into nucleosomes during the whole cell cycles. To date, histone variants of all canonical histone have been recognized, except for H4 (Maze et al. 2014). In higher eukaryotes, H2A family encompasses the largest number of variants, including macroH2A, H2A.Bbd, H2A.X and H2A.Z, in which H2A.Z is considered as the most evolutionarily conserved one (van Daal et al. 1990; Thatcher and Gorovsky 1994). H2A.Z and H2A have typically ~60% sequence similarity (see Figure 1 for an example). H2A.Z differs from H2A in the increased acidic patch and the carboxy-terminal α-helix included in the docking domain (Figure 1), which is a structure involved in the interaction of the H2A-H2B dimer with the $(H3\text{-}H4)_2$ tetramer (Luger et al. 1997; Suto et al. 2000).

H2A.Z has been identified by different names in various species, including hv1 in *Tetrahymena thermophila* (White et al. 1988), HTA8, HTA9, and HTA11 in *Arabidopsis thaliana* (March-Díaz and Reyes 2009), Htz1 in *Saccharomyces cerevisiae* (Jackson et al. 1996), H2Az in *N. crassa* (Hays et al. 2002), or H2Av in *Drosophila melanogaster*, for example. Within these different organisms, H2A.Z variants show high levels of sequence similarity. Conservation of H2A.Z throughout evolution indicates that it plays important roles in eukaryotic cells, that cannot be replaced by H2A. Actually, the absence of H2A.Z has been reported as lethal in many organisms such as mouse (Faast et al. 2001), *Drosophila* (van Daal and Elgin 1992), frogs and *Tetrahymena* (Liu et al. 1996), but not in *S. cerevisiae* in which deletion of H2AZ stops nonetheless cell cycle progression (Jackson and Gorovsky 2000; Adam et al. 2001). Across eukaryotes, H2A.Z has been found to be involved in a diverse range of biological processes, including genome stability (Downs et al. 2004; Krogan et al. 2004; Keogh et al. 2006), DNA repair (Kalocsay et al. 2009; Xu et al. 2012; Alatwi and Downs 2015; Gursoy-Yuzugullu et al. 2015) and transcriptional regulation (Marques et al. 2010; Deal and Henikoff 2011; Soboleva et al. 2014). In filamentous fungi, current knowledge on the function of H2A.Z is scarce. One study about the function of H2A.Z in filamentous fungi was carried out on *Neurospora crassa*, finding that H2A.Z regulates oxidative stress response (Dong et al. 2018). However, even though chromatin structure changes are of major importance in regulating the biosynthesis of several SMs, the role of H2A.Z has been overlooked. Owing to the prominent role of filamentous fungi in pharmaceutical production, food safety, agriculture and the critical function of H2A.Z in various species, a better understanding on the role of chromatin dynamics mediated by H2A.Z in these fungi warrants no delay. In this review, we summarize current knowledge of H2A.Z functions with a focus on *Fusarium* spp. to lay the foundation for the further study of H2A.Z that will be carried out in these species.

H2A.Z in fungi

Proteomes of 43 fungi were searched for domains matching the HMM profile for the C-terminal end of H2A (HMMER3 and PFAMv32 profile PF16211, (Bateman et al. 2000; Eddy 2009), containing the hypervariable part of H2A vs. H2A.Z docking domain. The C-terminal end of H2A is known to play a crucial role in stabilizing nucleosome particles and recognition of the linker histone H1 (Vogler et al. 2010). The length and nature of the tail in both H2A and H2A.Z have a conserved function in regulating association with nucleosomes (Wratting et al. 2012). Here, at least two to five hits were obtained in all fungi analyzed (Supplemental Table S1), and putative H2A/H2A.Z identification was proposed from the examination of partial sequence alignment of C-termini of the identified H2A/H2A.Z (Supplemental Figure S1), containing most of the docking domain, and the derived phylogenetic tree (Figure 2; PhyML 3.3) (Guindon et al. 2010). Examining domain sequences in details (Supplemental Figure S1), among

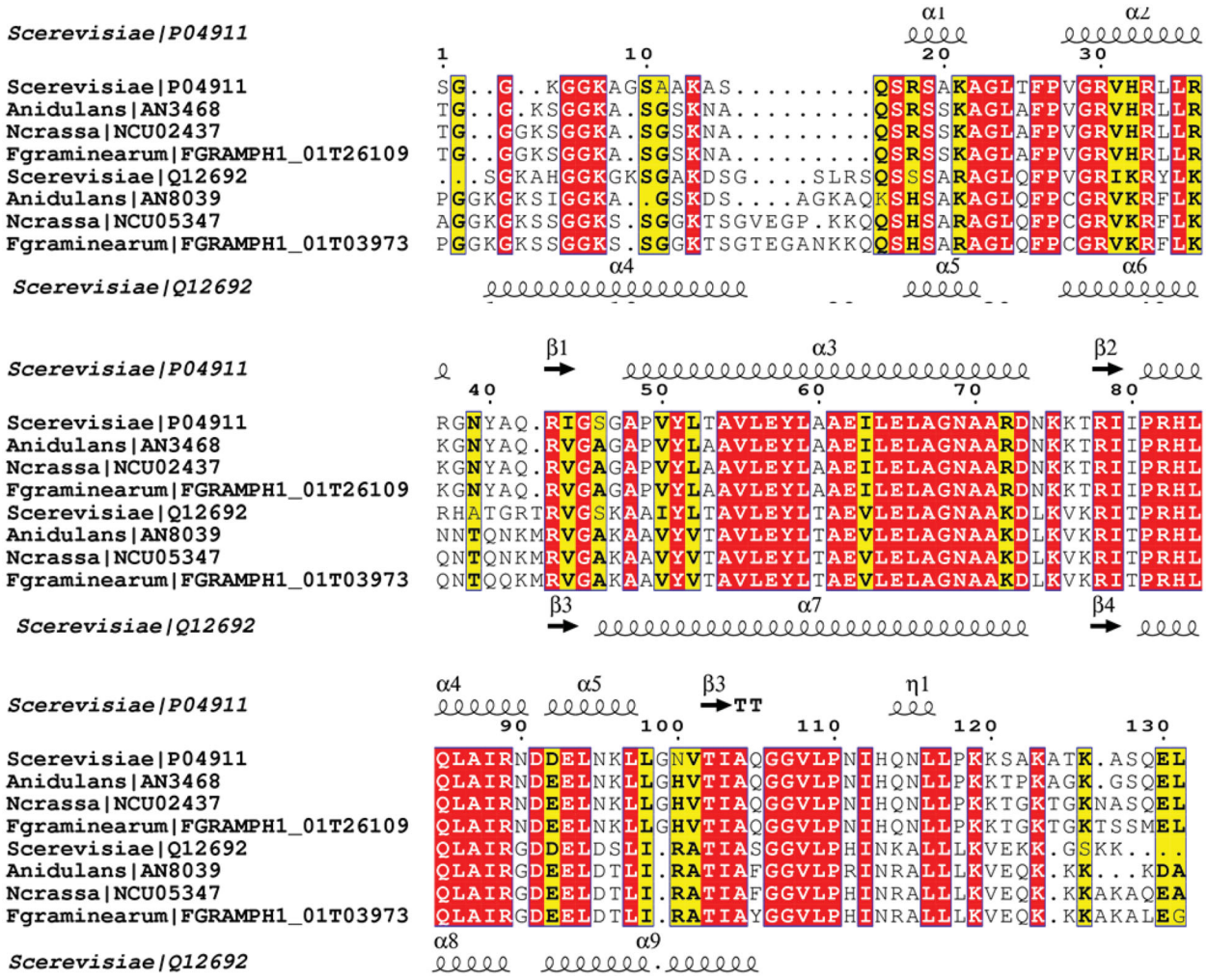


Figure 1. Sequence alignment of the whole protein sequences of H2A and H2A.Z from *S. cerevisiae*, *A. nidulans*, *N. crassa*, and *F. graminearum*. Sequences are numbered according to *S. cerevisiae* H2A (P04911) Alignment was performed with CLC Workbench 20.0 and secondary structures were predicted from *S. cerevisiae* H2A (P04911) and H2A.Z (Q12692) experimental models (PDB accession 1ID3 and 4M6B, respectively) using ESpript 3.0 (Robert and Gouet 2014). Identical residues are highlighted in red, highly similar ones are boxed in yellow. Helices are represented as squiggles, ß-strands with arrows, and turn as TT. H2A accessions: P04911, AN3468, NCU02437, FGRAMPH1_01T26109; H2A.Z accessions: Q12692, AN8039, NCU05347, FGRAMPH1_01T03973.

other differences, the presence of a glycine residue at position 99 (numbering according to *S. cerevisiae* H2A) seems to be a hallmark of H2A (versus H2A.Z). Conversely, the exchange of an asparagine for an aspartic acid in position 95 as well as the exchange of proline 118 for leucine are signatures of H2A.Z. All analyzed fungi but one were found to possess one histone H2A variant and one or more canonical H2A. Indeed, the Basidiomycota *Melampsora larici-populina*, the poplar leaf rust, hit on three proteins that all cluster with other H2A proteins. Regarding H2A, while all Pezizomycotina seem to possess one single H2A, yeasts and Basidiomycota have a varying number of them. Only the yeast *Yarrowia lipolytica* and the Basidiomycota *Ustilago maydis* are exceptions with one single H2A protein detected in their proteomes.

Chromatin remodelling complexes mediate H2A.Z exchange for H2A

Functions of H2A.Z in cells are linked to the dynamics of its deposition and removal from nucleosomes. These processes are mediated by several ATP-dependent chromatin remodelling complexes, often referred to as complexes belonging to the SWI/SNF or SNF2 superfamily (van Attikum et al. 2007; Gerhold and Gasser 2014). Typically, SNF2 proteins contain two conserved motives, the DEXDc (DEAD-like helicases) and HelicC (helicase superfamily c-terminal domain) subdomains, which together constitute the ATPase domain and can use the energy derived from ATP hydrolysis to modify chromatin structure (Lusser and Kadonaga 2003; Smith and Peterson 2005). This superfamily of proteins

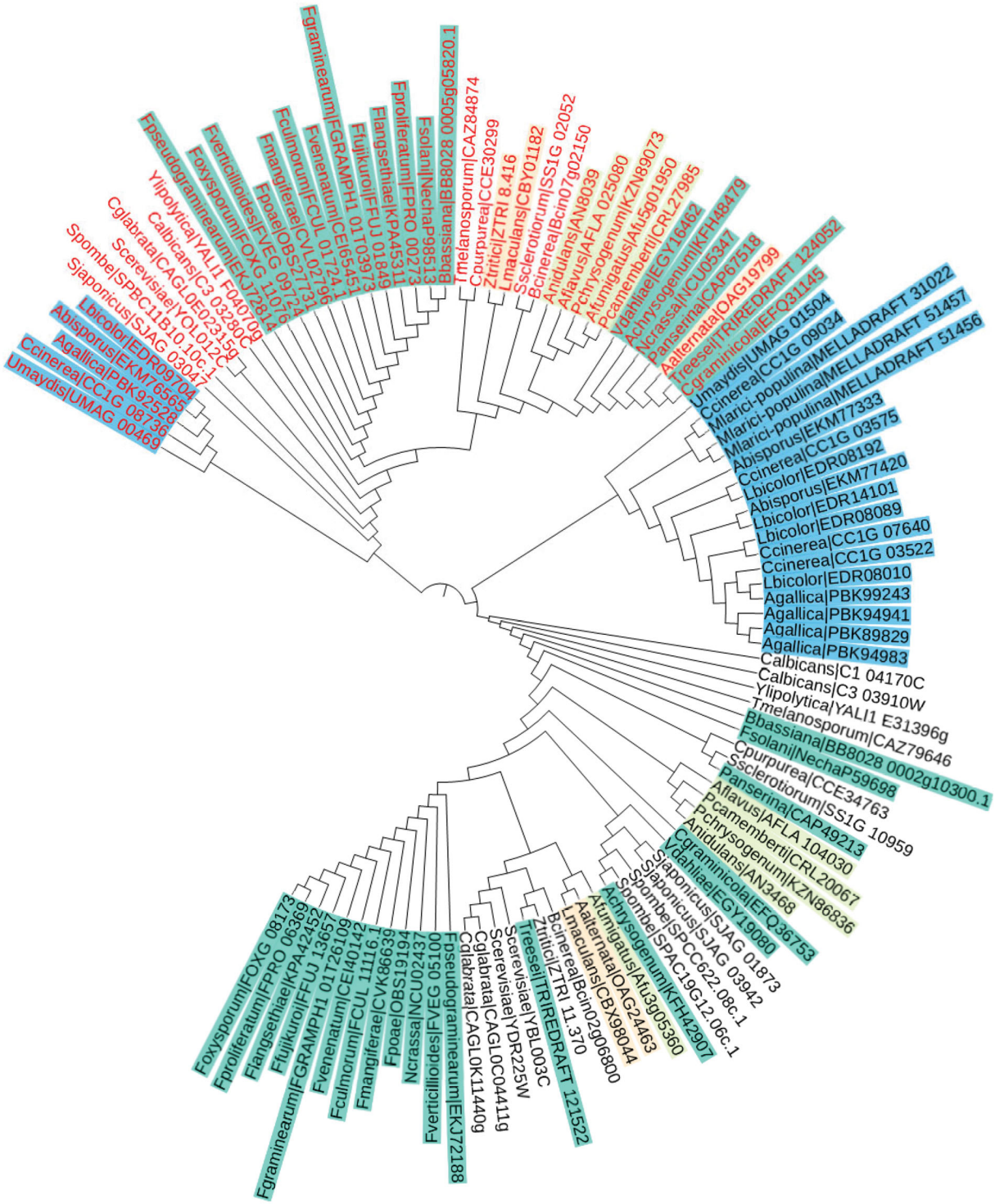


Figure 2. Phylogenetic tree based on H2A C-terminal domain homology. Domains were aligned with *hmmalign* programme from HMMER3 suite using the PFAM HMM model PF16211 (Bateman et al. 2000; Eddy 2009). Texts in red are H2A.Z, identified for their protein sequence homology with *S. cerevisiae* Htz1; texts in black are H2A, identified for their protein sequence homology with *S. cerevisiae* H2A. Texts with light green background are species belong to class Eurotiomycetes, dark green are species belong to class Sordariomycetes, blue are species belong division Basidiomycota, orange are species belong to class Dothideomycetes. Texts without background are other species.

consists of a large range of chromatin remodellers of varying functions, including histone dimer exchange (Ryan and Owen-Hughes 2011). Figure 3 is a schematic representation of yeast subunits of chromatin remodelling complexes SWR1, INO80, and NuA4 that relate to exchange of H2A.Z, histone post-translational

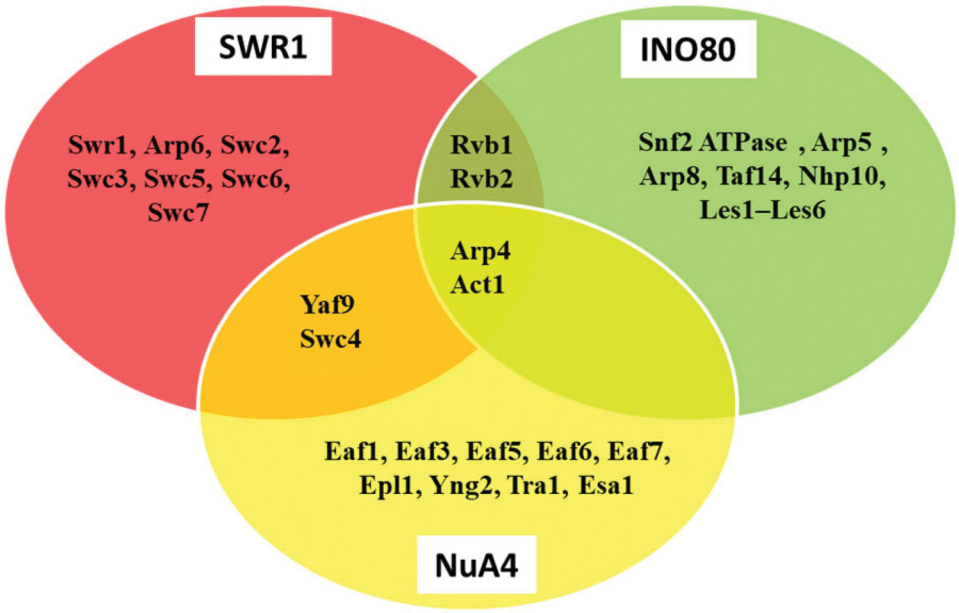


Figure 3. Proteins identified as subunits of SWR1, INO80 and NuA4 complexes in *S. cerevisiae*. Circles include subunits belonging to the complex indicated in the corresponding white tag. Overlaps between complexes are common subunits.

modification as well as DNA repair. Strikingly, several protein subunits are shared between the three complexes, for example, Arp4p and Act1p are found in all of them, reflecting the close association between SWR1, INO80 and NuA4 complex.

The SWR-C/SWR1 complex

In *S. cerevisae*, the complex SWR1 belonging to SNF2 family is involved in the deposition of H2A.Z (Kobor et al. 2004). It can replace H2A-H2B with H2A.Z-H2B dimers. Yeast SWR1 complex includes 13 subunits. Among them, Act1p, Arp4p, Swc4p, Rvb1p, and Rvb2p are essential for cell viability, since the absence of any of the respective coding genes is lethal for the organism. In contrast, subunits Swr1p (catalytic subunit), Yaf9p, Arp6p, Swc2p, Swc3p, Swc5p, Swc6p, and Swc7p are not essential but are required for optimal function of the complex (Krogan et al. 2003; Kobor et al. 2004; Mizuguchi et al. 2004). Complexes similar to the yeast SWR1 have been characterised in other organisms including mammalians and plants. In humans, two complexes seem related to SWR1, namely SRCAP and Tip60/p400. In SRCAP complex, the SNF2 protein SRCAP (SWI2/SNF2-related CBP activator protein) is identified as the ortholog of Swr1p, contributing to the recruitment of H2A.Z variants on nucleosomes (Houjian Cai et al. 2006; Ruhl et al. 2006; Wong et al. 2007). The Tip60/p400 complex contains several chromatin-modifying enzymes, such as p400 ATPase and the Tip60 histone acetyltransferase, which also shows high sequence resemblance to Swr1p and SRCAP (Ikura et al. 2000; Eissenberg, Wong, and Chrivia 2005). In *Drosophila*, the dTIP60 complex mediates the deposition of H2A.Z. The Domino protein, an ortholog of the yeast Swr1p, has been indicated as the catalytic subunit of the complex (Kusch et al. 2004).

The INO80 complex

H2A.Z can be actively removed from nucleosomes by chromatin remodellers. In yeast and human, the SWR1-related Inositol requiring 80 (INO80) complex can remove H2A.Z from nucleosomes (Morrison and Shen 2009; Tosi et al. 2013; Alatwi and Downs 2015). INO80 complex is another subfamily of the SNF2 family that shares several subunits with SWR1 complex, and is usually related to DNA double-strand break (DSB) repair (Clapier and Cairns 2009; Chen et al. 2013). In humans, ANP32E is a histone chaperone reported to function by removing H2A.Z (Mao et al. 2014; Obri et al. 2014). Homolog of INO80 has also been identified in *Arabidopsis*, in contrast with its function in yeast and animals, it preferentially facilitates the enrichment of H2A.Z at the ends of repressor genes, at the main floral Flowering Locus C (FLC) and MADS Affecting Flowering 4/5 (MAF4/5) (Zhang et al. 2015). Therefore, the roles of INO80 involving in H2A.Z exchange may be species or gene specific.

The NuA4 complex

The NuA4 histone acetyltransferase complex has a strong genetic and functional link with SWR1 complex.

They share four subunits including Arp4p, Act1p, Yaf9p and Swc4p (Figure 3). Additionally, the subunit Eaf1p has significant homology to Swr1p outside of the SWI/SNF-related ATPase domain (Auger et al. 2008; Altaf et al. 2010). In human and yeast, it was shown that the ability of SWR1 to replace canonical H2A from nucleosome by H2A.Z is greatly enhanced due to the prior acetylation of chromatin by NuA4, probably the subunit Eaf1p (Doyon and Côté 2004; Jin et al. 2005; Auger et al. 2008; Altaf et al. 2010). It was also observed that acetylation of histone H4 in yeast by Esa1p, the catalytic component of NuA4, is required for DNA double-strand break repair (Bird et al. 2002).

Homologs of most subunits of *S. cerevisiae* SWR1, INO80, NuA4 complexes can be found in filamentous fungi, such as in the sordariomycetes *N. crassa* and *F. graminearum* and the eurotiomycete *A. nidulans* (Table 1). Protein sequences of *S. cerevisiae* Swr1p (belongs to SWR1 complex), Snf2p (belongs to INO80 complex) and Esa1p (belongs to NuA4 complex) were aligned (Figure 4; Supplemental Figures S2, S3, and S4). These proteins are identified as catalytic subunits of each complex. As shown in the results, highly conserved regions of the three proteins can be found in all fungi investigated. We believe that similar processes of H2A.Z exchange also occur in filamentous fungi. However, details of the process may differ from *S. cerevisiae*, because compositions of SWR1, INO80 and NuA4 complex are not totally equal between these species. For example, homolog of Yng2p, an essential subunit of NuA4 in *S. cerevisiae*, which is important for the efficient acetylation of histone H4 or histone H2A, is not found in *N. crassa*, *A. nidulans*, and *F. graminearum*. Therefore, the already known functions and mechanisms of H2A.Z exchange in any other species including yeast cannot be copied directly to filamentous fungi. The potential role of H2A.Z in filamentous fungi needs further investigation.

Post-translational modifications of H2A.Z

PTMs such as acetylation, phosphorylation, methylation, ubiquitylation and sumoylation have been abundantly described on N-terminal tails of canonical histones. They would influence the overall chromatin state by altering inter-nucleosomes interactions and finally regulate gene expression (Bannister and Kouzarides 2011; Audia and Campbell 2016). Similarly, PTMs also occur on the histone variant H2A.Z, leading to differences in the biochemical properties of H2A.Z-containing nucleosomes and marking functional regions of chromatin (Hu et al. 2011; Binda et al. 2013). N-terminal tail of H2A.Z is extensively acetylated on lysines K4, K7, K11 and K13, correlating with gene activation (Bruce et al. 2005; Boyne et al. 2006; Ku et al. 2012; Valdés-Mora et al. 2012; Hu et al. 2013). NuA4 is a histone acetyltransferase complex that shares several subunits with the SWR1 and INO80 complex (Figure 3). Their primary acetylation targets are lysines of histone H4. More recently, the function of NuA4 was shown to also involve the acetylation of H2A.Z (Smith et al. 1998; Allard et al. 1999; Keogh et al. 2006).

H2A.Z can also be mono-ubiquitinated at lysines K120, K121, and K125, mediated by the Polycomb Repressive Complex 1 (PRC1) (Sarcinella et al. 2007; Draker et al. 2011; Ku et al. 2012). This modification is generally considered as a silencing mark and appears to occur solely in mammals (Sarcinella et al. 2007). SUMO (Small Ubiquitin-like MOdifier) proteins are similar to ubiquitin and can also be covalently linked to lysines (Sevilla and Binda 2014). In *S. cerevisiae*, H2A.Z can be SUMOylated at lysines 126 and 133, and play an important role in DNA repair by relocating unrepaired chromosomal breaks to nuclear periphery (Kalocsay et al. 2009).

H2A.Z further regulates gene expression through collaborating with other histone marks, particularly those on H3. For example, both in human and mouse embryonic stem (ES) cells, H2A.Z is co-localized with trimethylation of K4 (H3K4me3) and K27 (H3K27me3) of histone H3 at both promoters and enhancers of genes involved in cell differentiation. In eukaryotic cells, H3K4me3 could create higher chromatin accessibility and is normally associated with transcriptional activation, while H3K27me3 is considered to mediate gene silencing (Santos-Rosa et al. 2002; Creyghton et al. 2008; Ku et al. 2012; Hu et al. 2013). In contrast, reduced H2A.Z deposition at the anthocyanin biosynthesis genes in *Arabidopsis* is accompanied by a great increase in H3K4me3 but a decrease in H3K27me3, consistent with enhanced expression levels (Carter et al. 2018; Hanyang Cai et al. 2019). Moreover, it seems that H2A.Z can act as a functional substitute for H3K9me3 in chromatin for the recruitment of Heterochromatin Protein 1 (HP1) (Ryan and Tremethick 2018).

Recent studies indicated that SMs of many filamentous fungal are regulated by epigenetic modifications. Among them, histone methylation becomes the major currently known methods of modification. Even though deletion of HP1, which is linked with H3K9me3 and H2A.Z, did not show any cytological or morphological defect in *F. graminearum*, whereas HP1 is required for normal growth in *N. crassa (Freitag* et al. 2004*)*, several SM gene clusters were up or down regulated (Reyes-Dominguez et al. 2012). For example, in the HP1

Table 1. Genes encoding subunits of chromatin remodelling complex SWR1, INO80, NuA4 in yeast and their homologs in *N. crassa*, *A. nidulans*, and *F. graminearum*[a].

S. cerevisiae			*N. crassa*	*A. nidulans*	*F. graminearum*
Proteins	Gene ID	Product description	Gene ID	Gene ID	Gene ID
Swr1p	YDR334W	Chromatin-remodelling protein SWR1	NCU09993	AN9077	FGRAMPH1_01G18675
Arp6p	YLR085C	Actin-related protein	NCU05587	AN7009	FGRAMPH1_01G09171
Swc2p	YDR485C	Htz1p-binding component of the SWR1 complex	NCU06453	AN7475	FGRAMPH1_01G06047
Swc3p	YAL011W	Htz1p-binding component of the SWR1 complex	NCU09105	–	–
Swc5p	YBR231C	Htz1p-binding component of the SWR1 complex; protein abundance increases in response to DNA replication stress;	NCU06491	AN0966	FGRAMPH1_01G24481
Swc6p	YML041C	Htz1p-binding component of the SWR1 complex; required for vacuolar protein sorting	–	–	–
Swc7p	YLR385C	Component of the SWR1 complex that incorporates Htz1p into chromatin	–	–	–
Snf2p	YOR290C	Catalytic subunit of the SWI/SNF complex; involved in transcriptional regulation; contains DNA-stimulated ATPase activity	NCU06488	AN2278	FGRAMPH1_01G24477
Arp5p	YNL059C	promotes nucleosome shifts in the 3 prime direction	NCU06394	AN2487	FGRAMPH1_01G20187
Arp8p	YOR141C	has mRNA binding activity	NCU06238	AN5911	FGRAMPH1_01G22879
Taf14p	YPL129W	involved in RNA polymerase II transcription initiation and in chromatin modification; contains a YEATS domain	NCU00444	AN0083	FGRAMPH1_01G14509
Nhp10p	YDL002C	Non-essential INO80 complex subunit; preferentially binds DNA ends, protecting them from exonucleatic cleavage;	–	–	FGRAMPH1_01G23115
Les1p	YFL013C	relocalizes to the cytosol in response to hypoxia	NCU01362	AN10560	FGRAMPH1_01G24503
Les2p	YNL215W	associates with the INO80 complex under low-salt conditions; protein abundance increases in response to DNA replication stress	NCU01534	AN6260	FGRAMPH1_01G15023
Les3p	YLR052W	Subunit of the INO80 complex	–	–	–
Les4p	YOR189W	target of the Mec1p/Tel1p DNA damage signalling pathway; proposed to link chromatin remodelling to replication checkpoint responses	–	–	–
Les5p	YER092W	Non-essential INO80 complex subunit; deletion affects telomere maintenance via recombination	–	–	–
Les6p	YEL044W	involved in regulation of chromosome segregation and maintenance of normal centromeric chromatin structure;	NCU06395	AN2485	FGRAMPH1_01G20191
Eaf1p	YDR359C	acts as a platform for assembly of NuA4 subunits into the native complex; required for initiation of pre-meiotic DNA replication,	NCU07863	AN4472	FGRAMPH1_01G18101
Eaf3p	YPR023C	Component of the Rpd3S histone deacetylase complex; nonessential component of the NuA4 acetyltransferase complex	NCU06787	AN1976	FGRAMPH1_01G19347
Eaf5p	YEL018W	Non-essential subunit of the NuA4 complex; Esa1p-associated factor	-	-	-
Eaf6p	YJR082C	Subunit of the NuA4; this complex acetylates histone H4 and NuA3 acetyltransferase complex that acetylates histone H3	NCU03289	AN2935	FGRAMPH1_01G02731
Epl1p	YFL024C	conserved region at N-terminus is essential for interaction with the NPC (nucleosome core particle); required for autophagy	NCU03834	AN6567	FGRAMPH1_01G24745
Yng2p	YHR090C	positions Piccolo NuA4 for efficient acetylation of histone H4 or histone H2A;	-	-	-
Tra1p	YHR099W	Subunit of SAGA and NuA4 complexes; interacts with acidic activators (e.g. Gal4p) which leads to transcription activation;	NCU01379	AN12431	FGRAMPH1_01G19463
Esa1p	YOR244W	Catalytic subunit of the NuA4; acetylates four conserved internal lysines of histone H4 N-terminal tail and can acetylate histone H2A; master regulator of cellular acetylation balance	NCU04782	AN5640	FGRAMPH1_01G10071
Arp4p	YJL081C	Nuclear actin-related protein involved in chromatin remodelling; component of chromatin-remodelling enzyme complexes	NCU02555	AN7441	FGRAMPH1_01G02187
Act1p	YFL039C	Actin; structural protein involved in cell polarisation, endocytosis, and other cytoskeletal functions	NCU04173	AN6542	FGRAMPH1_01G24551
Rvb1p	YDR190C	ATP-dependent DNA helicase; conserved component of multiple complexes including the INO80 complex, the Swr1 complex, and the R2TP complex (Rvb1-Rvb2-Tah1-Pih1)	NCU03482	AN1971	FGRAMPH1_01G17223
Rvb2p	YPL235W	similar to Rvb1p	NCU06854	AN0327	FGRAMPH1_01G19889
Swc4p	YGR002C	incorporates Htz1p into chromatin; component of the NuA4 histone acetyltransferase complex	NCU04002	AN4445	FGRAMPH1_01G07207
Yaf9p	YNL107W	may function to antagonise silencing near telomeres; interacts directly with Swc4p	NCU00359	AN1859	FGRAMPH1_01G23049

[a]Red: subunits of SWR1 complex; green: subunits of INO80 complex; yellow: subunits of NuA4 complex; blue: subunits shared by these three complexes; grey: subunits shared by SWR1 and NuA4 complex; purple: subunits shared by INO80 and SWR1 complex.

deletion mutant of *F. graminearum*, the expression of AUR genes required for the production of the pigment aurofusarin was greatly enhanced, while gene expression and metabolites involved in the deoxynivalenol (DON) pathway were inhibited. However, the absence of HP1 led to an increase of the heterochromatic mark H3K9me3 in both gene clusters (Reyes-Dominguez et al. 2012). In *F. verticillioides*, mutants lacking *Dim5* (or *Kmt1*), a lysine histone methyltransferase enzyme mediating H3K9me3 deposition, showed significant defects in fungal development and pathogenicity but increased tolerance to osmotic stress (Gu et al. 2017). Anothertwo

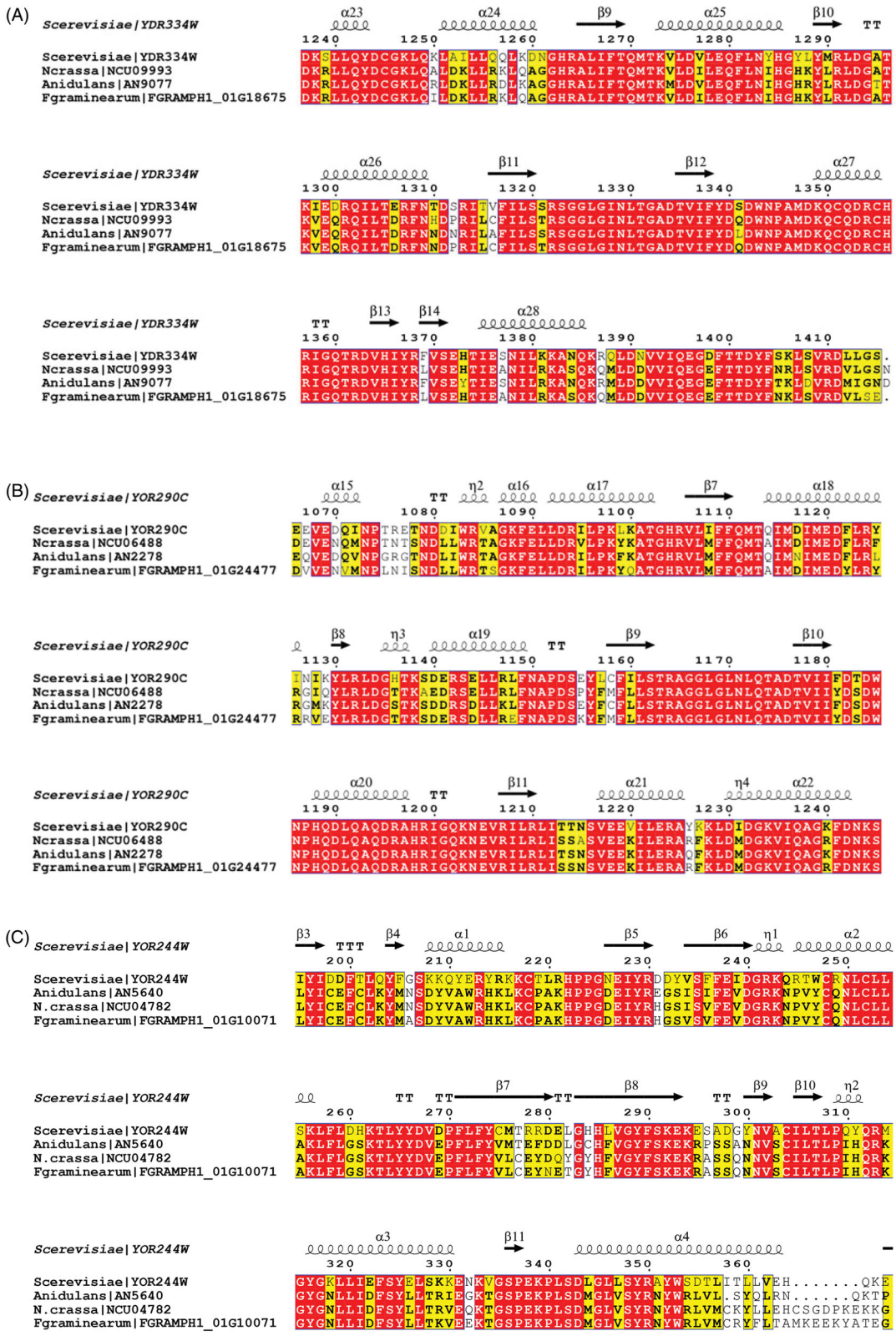


Figure 4. Partial alignments of conserved domains of subunits Swr1p (A), Snf2p (B) and Esa1p (C) in *S. cerevisiae*, *N. crassa, A. nidulans,* and *F. graminearum*. A. DEAD-box domains (Helicase_C PFAM PF00271) of subunits Swr1p. B. DEAD-box domains (Helicase_C PFAM PF00271) of subunits Snf2p. C. MOZ_SAS (PF01853) found in acetyltransferases. For all alignments, sequences are numbered according to *S. cerevisiae* sequences. Alignments were performed with CLC Workbench 20.0 and secondary structures were predicted from *S. cerevisiae* Swr1p, Snf2p, and Esa1p experimental models (PDB accession 6GEJ, 5Z3L, and 1MJA, respectively) using ESpript 3.0. Identical residues are highlighted in red, highly similar ones are boxed in yellow. Helices are represented as squiggles, ß-strands with arrows, and turn as TT. Gene IDs are listed in Table 1. Full alignments are proposed in Supplemental Figures S2, S3, and S4.

histone PTMs, H3K4me2/3 and H3K27me3, which have been proved to co-localize with H2A.Z, also play critical roles in the regulation of SMs production in filamentous fungi (Connolly et al. 2013; Liu et al. 2015). H3K4me2 is indeed required for the active transcription of genes involved in DON and aurofusarin biosynthesis in *F. graminearum*, although H3K4me3 is dispensable for DON production (Liu et al. 2015). In the same species, ChIP-sequencing showed that extensive segments, covering a third of the genome, were enriched with H3K27me3 (Connolly et al. 2013). Removal of the mark by mutation of the methyltransferase subunit (KMT6) resulted in the activation of more than 1500 genes, predominantly genes involved in the production or detoxification of SM or predicted to play a role in pathogenicity. Thus, H3K27me3 acts as a repressor of genes in *F. graminearum* (Connolly et al. 2013). In *F. fujikuroi*, KMT6 appears to be essential. Knock down of KMT6 reduced H3K27me3 levels at the respective gene *loci* and induced four otherwise silent putative SM gene clusters accompanied by the accumulation of novel metabolites (Studt et al. 2016).

In summary, H2A.Z deposition or eviction on chromatin is associated with various PTMs such as H3K4me3, H3K27me3 to control the accessibility of chromatin. In filamentous fungi, even though no research has been carried out to investigate whether H2A.Z functions in SM production, more and more studies provide evidence that histone PTMs are key factors involved in these pathways. We hypothesize that H2A.Z also plays major roles in filamentous fungi to regulate the biosynthesis of SMs.

H2A.Z in controlling gene transcription

Roles of H2A.Z in controlling gene transcription have been extensively studied in humans, *Drosophila melanogaster*, *A. thaliana* and budding yeast, and recently reviewed with a focus on its action in gene regulation (Giaimo et al. 2019). According to genome-wide localization maps of H2A.Z, nucleosomes containing H2A.Z are widespread in the organisms analyzed, but the distribution and density of H2A.Z vary between different chromosomes (Leach et al. 2000; Zhang et al. 2005; Guillemette and Gaudreau 2006). It is indicated that H2A.Z variant is preferentially enriched at the regions of transcriptional start sites (TSS) (Raisner et al. 2005; Guillemette and Gaudreau 2006; Mavrich et al. 2008; Zilberman et al. 2008), which suggested a relationship between H2A.Z and gene transcription. However, significant arguments still exist about whether and how this histone variant is involved in transcriptional regulation.

RNA polymerase II (RNAPII) is a multiprotein complex found in eukaryotic cells which catalyzes the transcription of DNA to synthesize precursors of mRNA and most snRNA and microRNA (Kornberg 1999; Sims et al. 2004). As a general transcription factor, the TATA-binding protein (TBP) binds specifically to a DNA sequence called the TATA box in the promoter region of genes to initiate the recruitment of other factors required for RNA Pol II to begin transcription (Kornberg 2007). In yeast, RNAPII and TBP could not be efficiently recruited to *GAL1-10* promoter in cells lacking H2A.Z (Adam et al. 2001). Meanwhile, the elongation rate of RNAPII was slower in the absence of H2A.Z (Santisteban et al. 2011). Generally, the entry site of the first (+1) nucleosome is a larger barrier for RNAPII transiting for essentially all genes in *Drosophila*, while gene body nucleosomes are low barriers. Therefore, RNAPII would stall both at the entry site and near the dyad axis. Notably, H2A.Z enrichment at the +1 nucleosome correlates with decreased RNAPII stalling and depletion of H2A.Z from a nucleosome position results in a higher barrier to RNAPII, suggesting that the high-energy barrier to RNAPII progression can be tuned by H2A.Z deposition. Meanwhile, H2A.Z incorporation at the +1 nucleosome regulates productive elongation by facilitating H2A.Z/H2B dimer loss without depletion of $(H3\text{-}H4)_2$ tetramers as H2A.Z levels anti-correlate with nucleosome turnover (Weber et al. 2014; Subramanian et al. 2015). Thus, H2A.Z deposition acts as an activator of gene transcription. Consistent with this idea, during the induced somatic cell reprogramming of mice, increased level of H2A.Z was detected in the high expressed genes involved in response to stress (hypoxia, oxygen levels, steroid hormone stimulus). Furthermore in mice, Rispal et al. (2019) found that decrease of H2A.Z at promoters inhibits the binding of the CDX2 intestine-specific transcription factor. The authors proposed that genes containing H2A.Z can be easily marked as active signals for the recruitment of acetyltransferase enzyme complexes and supply access for the binding of transcription factors (Peserico and Simone 2011; Dong et al. 2016). However, a recent study in *N. crassa* revealed that H2A.Z is present at TSS of the oxidative stress resistant gene *catalase-3* and function as a negative regulator (Dong et al. 2018). Under non-inductive condition, H2A.Z counteracts the positive effects of the transcription factor at cat-3 *locus*, CPC1, to achieve low level of cat-3 expression. Upon oxidative stress, H2A.Z is rapidly evicted from cat-3 locus to facilitate the recruitment of CPC1, contributing

to robust and full cat-3 gene expression in response to external stimuli. Therefore, H2A.Z is here regarded as barrier for RNAPII transiting (Dong et al. 2018).

The deposition of H2A.Z also relates to DNA methylation, one of several epigenetic marks that cells use to control negatively gene transcription. In *A. thaliana*, it is reported that H2A.Z prevents genes from DNA methylation and reduce gene activity. Meanwhile, H2A.Z can also be excluded from the site of DNA methylation in the bodies of actively transcribed genes and in methylated transposons to affect gene silencing (Zilberman et al. 2008). Recently, however, further study demonstrated that there is only minor influence on the level of DNA methylation in a novel H2A.Z loss-function line of *A. thaliana* (Coleman-Derr and Zilberman 2012). In addition, the highest and lowest expressed genes have the least H2A.Z enrichment near TSS. Within gene bodies, H2A.Z deposition positively regulates gene responsiveness, but may negative correlates with gene constitutive expression. The authors suggested that a major function of gene body DNA methylation is to prevent the incorporation of H2A.Z within gene bodies, and thus stabilize the expression of constitutive genes, and on the other hand H2A.Z deposition within unmethylated gene bodies could promote the expression of inducible genes, including genes response to developmental, biotic and abiotic stimuli (Coleman-Derr and Zilberman 2012). More recently, another study on *A. thaliana* also suggested that H2A.Z in gene bodies has a strong repressive effect on transcription, whereas in +1 nucleosomes, it is important for maintaining the activity of some genes (Sura et al. 2017). These findings are consistent with results in yeast indicating that H2A.Z incorporates in coding regions of genes that are involved in genotoxic stress responses (Sadeghi et al. 2011). In addition, Hartley and Madhani (2009) found in budding yeast that H2A.Z deposition is dispensable for nucleosome positioning, while the establishment of nucleosome-free region is necessary for H2A.Z deposition. Finally, another study in yeast demonstrated that H2A.Z is selectively enriched at 5′ regions of both active and inactive genes (Raisner et al. 2005). No correlation between the levels of H2A.Z deposition and either the transcription rate or RNA polymerase II occupancy can be observed (Raisner et al. 2005). Therefore, role of H2AZ in controlling gene transcription appears to be versatile and highly dependent on chromatin context.

Roles of H2A.Z on DNA repair

DNA double-strand breaks (DSB) occur as a result of genome damage, and cells have developed two major repair pathways: homologous recombination (HR) and the non-homologous end joining (NHEJ) (Hiom 2010; Grabarz et al. 2013). During DSB repair, a relaxed and open chromatin domain is required to facilitate the loading of repair factors (Kim et al. 2007; Sartori et al. 2007). Before the recruitment of 53BP1p and brca1p in the NHEJ pathway, components binding to the break site contain a variety of factors including MRX (MRN) complex and Ku proteins Ku70 and Ku80 (Daley and Sung 2014). HR pathway is also initiated by the MRX complex in particular, then followed by the recruitment of other factors including such as RAD51 protein (Chatterjee and Walker 2017). In budding yeast, strains lacking the subunit of INO80 complex Ino80p, Arp5p, or Arp8p are hypersensitive to DNA damaging agents and to DSBs induced by the HO endonuclease (Attikum et al. 2004). ChIP experiments showed that Ino80p, Arp5p, and Arp8p are recruited to an HO-induced DSB, where a phosphorylated form of H2A accumulates, indicating that INO80-mediated chromatin remodelling appears to facilitate processing of the DSBs repair (Attikum et al. 2004). Another study in yeast found H2A.Z is rapidly but transiently deposited at the break area and it is involved in DSB tethering. Meanwhile, H2A.Z SUMOylation is needed for DSB relocation (Kalocsay et al. 2009). In human 293 T cells, H2A.Z seems to be directly involved in the regulation of DSB repair through the HR and NHEJ pathway (Xu et al. 2012). It was observed rapidly and reversibly exchanged by p400 motor ATPase onto a unique DSB, promotes the acetylation and ubiquitination of histones, function together to shift the chromatin to an open domain at the site of DSB damage, therefore helps the loading of brca1 complex (Xu et al. 2012). H2A.Z exchange also restricts single-stranded DNA production by nucleases and is essential for loading of the Ku70/Ku80 DSB repair protein (Xu et al. 2012). Further analyses showed that, in mammalian cells, the deposition of H2A.Z on nucleosomes at DSBs is transient; it can be removed from chromatin flanking DNA damage by INO80 and histone chaperone Anp32e rapidly, which promotes DSB repair (Alatwi and Downs 2015; Gursoy-Yuzugullu et al. 2015). Here, the authors propose the rapid eviction of H2A.Z releases H4 tail for acetylation, thus disrupting interactions between nucleosomes, contributing to an open and flexible chromatin. By contrast, Taty-Taty et al. (2014) found the absence of H2A.Z impaired cell proliferation and viability but did not lead to any DSB repair defects in the osteosarcoma U2OS cell lines and T-immortalized human fibroblasts. There was also no H2A.Z recruitment around DSBs that could be detected (Taty-Taty et al. 2014). Different ways of obtaining

H2A.Z depletion may help explain the controversy. Xu et al. used shRNA to achieve a long-term and robust depletion, while Taty-Taty et al. only obtained a partial reduction in H2A.Z expression. Taken together, these studies revealed that H2A.Z plays a critical role in remodelling chromatin structure at DSBs. The underlying molecular mechanism might be that H2A.Z is actively accumulated on nucleosomes at DSBs. However, the H2A.Z-H2B dimer could be rapidly removed by INO80 complex and the histone chaperone ANE32E, resulting in loss of acidic patch and release of the H4 tail for acetylation by Tip60. Histone acetylation at DSBs can create a more open conformation of chromatin and further promotes ubiquitylation, which is necessary for the loading of braca1.

In filamentous fungi, many homologs of DNA repair factors of *S. cerevisiae* have been identified. For example, genetic and molecular analyses of *Neurospora* mutants revealed that MEI-3 (homolog of RAD51p), MUS-51 and MUS-52 (homologs of Ku70p and Ku80p) are involved in the HR and NHEJ pathway, respectively (Hatakeyama et al. 1995; Ninomiya et al. 2004; Ishibashi et al. 2006). Compared to yeast, HR frequencies in filamentous fungi are extremely low, meaning that DNA DSBs are predominantly repaired by NHEJ, which makes generation of gene knock-out mutants by HR time-consuming Ishibashi et al. 2006; (Nielsen et al. 2006; Nielsen, Nielsen, and Mortensen 2008). Therefore, studies have been extensively carried out to increase the efficiency of gene targeting by inhibiting NHEJ. Indeed, better success at gene targeting has been observed in KU-deficient mutants of *N. crassa*, *Aspergillus nidulans*, *A. fumigatus*, *A. sojae*, *A. oryzae*, and *Cryptococcus neoformans*. Taking into account the roles of H2A.Z in HR and NHEJ pathway in other organisms including yeast, maybe it is another potential target for the optimization of gene targeting in filamentous fungi.

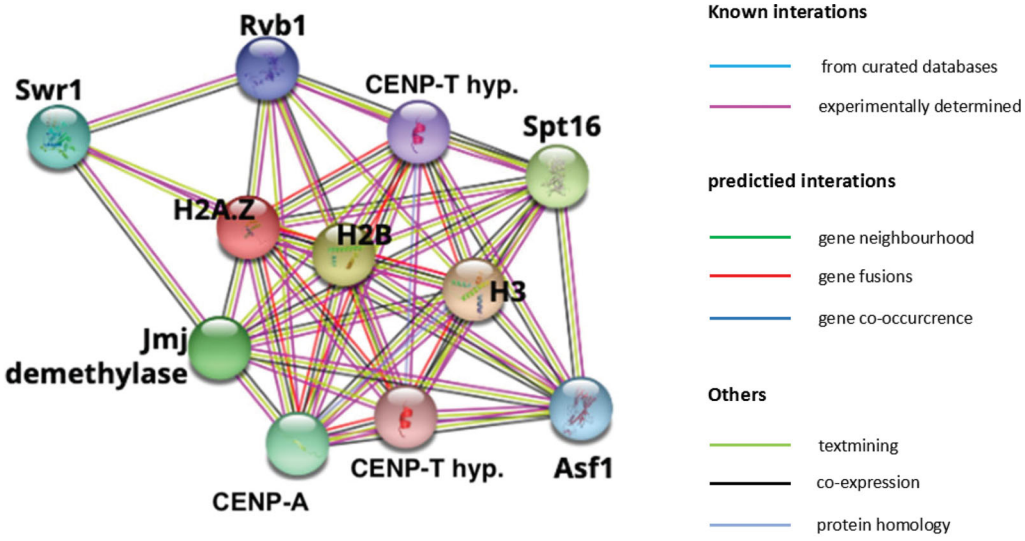
H2A.Z affects nucleosome stability

Within the nucleosome, histone-histone or histone-DNA interactions play an important role in the stability of the entire particle. In some cases, H2A.Z stabilizes nucleosome structure (Park et al. 2004; Thambirajah et al. 2006; Jin and Felsenfeld 2007). When using fluorescence resonance energy transfer (FRET) to compare nucleosomes containing the histone variant H2A.Z with canonical nucleosomes containing replication-dependent major histones, the dissociation of the (H2A.Z-H2B) dimer from the nucleosome occurs at higher salt concentrations, and over a broader salt range compared with the (H2A-H2B) dimer. A similar study revealed that H2A.Z could stabilize chromatin, but it is dependent on the acetylation of core histones (Thambirajah et al. 2006). Jin and Felsenfeld (2007) reported that all nucleosome core particles (NCPs) contain H3.3 reduced stability compared with H3 NCPs. in addition, NCPs that contain both H3.3 and H2A.Z are even less stable than NCPs containing H3.3 and H2A. Intriguingly, NCPs containing H3 and H2A.Z are at least as stable as H3/H2A NCPs. By contrast, some studies indicated that even though the crystal structure of NCP containing H2A.Z is similar to that of the nucleosome structure containing major histone proteins, histone H2A.Z variant may result in subtle destabilization of chromatin, which may be important for transcriptional activation (Suto et al. 2000; Abbott et al. 2001; Zhang et al. 2005). The partners of H2A.Z within NCP may thus be key factors in determining nucleosome stability (Jin and Felsenfeld 2007). When H2A.Z is coupled with H3, it might form an unusually stable chromatin conformation. Otherwise, it may destabilize the nucleosomes. Such characteristics are consistent with the physiological roles of H2A.Z, especially its involvement in the transcriptional regulation and DNA repair.

In fungi, most of the studies of NCP focus on *S. cerevisiae*; the NCP of filamentous fungi has been much less characterized. Using predicted-predicted protein interactions based on knowledge transfer from other eukaryotes (Szklarczyk et al. 2019), H2A.Z is likely to interact extensively with other proteins through both direct or indirect ways in *F. graminearum* (Figure 5; Letunic et al. 2015; Letunic and Bork 2018). For example, according to this network, the relationship between H2A.Z and Swr1p has been experimentally determined in yeast and humans, while it is predicted to co-occur with RuvB-like helicase1, histone H4 as well as an uncharacterized protein. There is also a co-expression with histone H2B and H3 (Figure 5). In future studies on roles of H2A.Z in controlling nucleosome stability, validating such predictions in filamentous fungi and taking into account the interaction of H2A.Z with other proteins may enlighten us more on the functions fulfilled.

Conclusions

Chromatin is a highly dynamic architecture mainly controlled by three ways, including ATP-dependent chromatin remodelling, histone variants and PTMs, and DNA methylation. H2A.Z is a highly conserved histone variant which can be deposited or removed from chromatin by the chromatin remodelling complex SWR1 or INO80, respectively. This process is accompanied by various histone PTMs as well as the conditions of DNA



Gene name	Annotation	Gene ID
H2A.Z	Histone Variant H2A.Z	FGRAMPH1_01G03973
H2B	Histone H2B	FGRAMPH1_01G26111
H3	Histone H3	FGRAMPH1_01G14931
Spt16	FACT complex subunit SPT16	FGRAMPH1_01G07139
CENP-T hypothetical	Histone H4 partial	FGRAMPH1_01G14929
Rvb1	RuvB-like helicase 1	FGRAMPH1_01G17223
Asf1	Histone chaperone ASF1	FGRAMPH1_01G00927
Swr1	Helicase SWR1	FGRAMPH1_01G18675
jmJ demethylase	JmjC domain-containing histone demethylase; targets tri- and dimethylated H3K36; predicted	FGRAMPH1_01G03799
CENP-A	Histone H3 centromeric variant, putative	FGRAMPH1_01G06247
CENP-T hypothetical	Histone H4 partial	FGRAMPH1_01G18051

Figure 5. Predicted functional partners of H2A.Z in *F. graminearum*. FgH2A.Z (FGRAMPH1_01G03973P0) was used as query for The Simple Modular Architecture Research Tool (SMART; (Letunic et al. 2015; Letunic and Bork 2018) to predict the corresponding interacting network of proteins pulling data from the Protein-Protein Interaction Networks data base STRING (Szklarczyk et al. 2019) using default settings. Each node represents all the proteins produced by a single, protein-coding gene locus. Edges represent protein-protein associations colour coded by source of information (see legend in the figure).

methylation, finally leading to the change of chromatin state. Normally, a more opened, flexible chromatin is necessary for many biological processes such as gene transcription and binding of DSB repair factors. According to the studies mentioned above, the status of chromatin in response to H2A.Z exchange varies between organisms, gene types as well as locations, meaning that the function of H2A.Z is very likely context-specific. It can act as a positive regulator under certain conditions, but might also be a negative regulator. Specific properties of H2A.Z-containing nucleosomes also linked with the incorporation with other histones or histone variants. For example, it was suggested that nucleosomes containing both H2A.Z and H3.3 histone variants are much less stable than nucleosomes of other composition (Jin and Felsenfeld 2007).

In filamentous fungi, regulation of SMs biosynthesis is highly linked to patterns of deposition of epigenetic markers such as H3K27me3, H3K4me3, and HP1. According to previous studies carried out in other species, some of these markers always co-localize with H2A.Z, suggesting the potential role of H2A.Z involved in filamentous fungi. Indeed, in *N. crassa*, it is reported that under normal and oxidative stress conditions, H2A.Z antagonized the positive effect of the transcriptional activator CPC1 to regulate the expression of catalase-3, an oxidative resistant gene (Dong et al. 2018). To date, this is the only study that focuses on H2A.Z in

filamentous fungi. As illustrated above, homologs of yeast Swr1p, Snf2p and Esa1p subunits, which are involved in the deposition/removal/acetylation of H2A.Z, can be identified in both *F. graminearum* and *F. fujikuroi*. We guess that H2A.Z also plays critical roles in central biological processes of *Fusarium* species, including the secondary metabolism.

Acknowledgements

The authors thank Vance C. Huskins for his careful proofreading.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was funded by ANR Grant ANR-18-CE91-0006 to N. P. Z. C. held a doctoral fellowship from the China Scholarship Council.

References

Abbott DW, Ivanova VS, Wang X, Bonner WM, Ausió J. 2001. Characterization of the stability and folding of H2A.Z chromatin particles: implications for transcriptional activation. J Biol Chem. 276(45):41945–41949.

Adam M, Robert F, Larochelle M, Gaudreau L. 2001. H2A.Z is required for global chromatin integrity and for recruitment of RNA polymerase II under specific conditions. Mol Cell Biol. 21(18):6270–6279.

Alatwi HE, Downs JA. 2015. Removal of H2A.Z by INO80 promotes homologous recombination. EMBO Rep. 16(8): 986–994.

Alberti F, Foster GD, Bailey AM. 2017. Natural products from filamentous fungi and production by heterologous expression. Appl Microbiol Biotechnol. 101(2):493–500.

Allard S, Utley RT, Savard J, Clarke A, Grant P, Brandl CJ, Pillus L, Workman JL, Côté J. 1999. NuA4, an essential transcription adaptor/histone H4 acetyltransferase complex containing Esa1p and the ATM-related cofactor Tra1p. Embo J. 18(18):5108–5119.

Altaf M, Auger A, Monnet-Saksouk J, Brodeur J, Piquet S, Cramet M, Bouchard N, Lacoste N, Utley RT, Gaudreau L, et al. 2010. NuA4-dependent acetylation of nucleosomal histones H4 and H2A directly stimulates incorporation of H2A.Z by the SWR1 complex. J Biol Chem. 285(21): 15966–15977.

Attikum H. v, Fritsch O, Gasser SM. 2007. Distinct roles for SWR1 and INO80 chromatin remodeling complexes at chromosomal double-strand breaks. Embo J. 26(18): 4113–4125.

Attikum H. v, Fritsch O, Hohn B, Gasser SM. 2004. Recruitment of the INO80 complex by H2A phosphorylation links ATP-dependent chromatin remodeling with DNA double-strand break repair. Cell. 119(6): 777–788.

Audia JE, Campbell RM. 2016. Histone modifications and cancer. Cold Spring Harb Perspect Biol. 8(4):a019521.

Auger A, Galarneau L, Altaf M, Nourani A, Doyon Y, Utley RT, Cronier D, Allard S, CoTé J, 2008. Eaf1 is the platform for NuA4 molecular assembly that evolutionarily links chromatin acetylation to ATP-dependent exchange of histone H2A variants. Mol Cell Biol. 28(7):2257–2270.

Bannister AJ, Kouzarides T. 2011. Regulation of chromatin by histone modifications. Cell Res. 21(3):381–395.

Bateman A, Birney E, Durbin R, Eddy SR, Howe KL, Sonnhammer ELL. 2000. The Pfam protein families database. Nucleic Acids Res. 28(1):263–266.

Beggs S, James TC, Bond U. 2012. The PolyA tail length of yeast histone MRNAs varies during the cell cycle and is influenced by Sen1p and Rrp6p. Nucleic Acids Res. 40(6): 2700–2711.

Benítez T, Rincón AM, Limón MC, Codón AC. 2004. Biocontrol mechanisms of trichoderma strains. Int Microbiol: Off J Spanish Soc Microbiol. 7(4):249–260.

Binda O, Sevilla A, LeRoy G, Lemischka IR, Garcia BA, Richard S. 2013. SETD6 monomethylates H2AZ on Lysine 7 and is required for the maintenance of embryonic stem cell self-renewal. Epigenetics. 8(2):177–183.

Bird AW, Yu DY, Pray-Grant MG, Qiu Q, Harmon KE, Megee PC, Grant PA, Smith MM, Christman MF. 2002. Acetylation of histone H4 by Esa1 is required for DNA double-strand break repair. Nature. 419(6905):411–415.

Boyne MT, Pesavento JJ, Mizzen CA, Kelleher NL. 2006. Precise characterization of human histones in the H2A gene family by top down mass spectrometry. J Proteome Res. 5(2):248–253.

Bruce K, Myers FA, Mantouvalou E, Lefevre P, Greaves I, Bonifer C, Tremethick DJ, Thorne AW, Crane-Robinson C. 2005. The replacement histone H2A.Z in a hyperacetylated form is a feature of active genes in the chicken. Nucleic Acids Res. 33(17):5633–5639.

Cai H, Kauffman S, Naider F, Becker JM. 2006. Genomewide screen reveals a wide regulatory network for Di/Tripeptide utilization in *Saccharomyces cerevisiae*. Genetics. 172(3): 1459–1476.

Cai H, Zhang M, Chai M, He Q, Huang X, Zhao L, Qin Y. 2019. Epigenetic regulation of anthocyanin biosynthesis by an antagonistic interaction between H2A.Z and H3K4me3. New Phytol. 221(1):295–308.

Caracuel Z, Roncero MIG, Espeso EA, González-Verdejo CI, García-Maceira FI, Di Pietro A. 2003. The PH signalling transcription factor PacC controls virulence in the plant pathogen *Fusarium oxysporum*. Mol Microbiol. 48(3): 765–779.

Carter B, Bishop B, Ho KK, Huang R, Jia W, Zhang H, Pascuzzi PE, Deal RB, Ogas J. 2018. The chromatin remodelers PKL and PIE1 act in an epigenetic pathway that determines H3K27me3 homeostasis in Arabidopsis. Plant Cell. 30(6): 1337–1352.

Chatterjee N, Walker GC. 2017. Mechanisms of DNA damage, repair, and mutagenesis. Environ Mol Mutagen. 58(5): 235–263.

Chen M, Licon K, Otsuka R, Pillus L, Ideker T. 2013. Decoupling epigenetic and genetic effects through systematic analysis of gene position. Cell Rep. 3(1):128–137.

Clapier CR, Cairns BR. 2009. The biology of chromatin remodeling complexes. Annu Rev Biochem. 78:273–304.

Coleman-Derr D, Zilberman D. 2012. Deposition of histone variant H2A.Z within gene bodies regulates responsive genes. PLoS Genet. 8(10):e1002988.

Connolly LR, Smith KM, Freitag M. 2013. The Fusarium Graminearum histone H3 K27 methyltransferase KMT6 regulates development and expression of secondary metabolite gene clusters. PLoS Genet. 9(10):e1003916. Edited by H. D. Madhani.

Creyghton MP, Markoulaki S, Levine SS, Hanna J, Lodato MA, Sha K, Young RA, Jaenisch R, Boyer LA. 2008. H2AZ is enriched at polycomb complex target genes in ES cells and is necessary for lineage commitment. Cell. 135(4): 649–661.

Daal A. V, Elgin SC. 1992. A histone variant, H2AvD, is essential in Drosophila Melanogaster. Mol Biol Cell. 3(6): 593–602.

Daal van A, EM White, SC, Elgin, MA. Gorovsky 1990. Conservation of intron position indicates separation of major and variant H2As is an early event in the evolution of eukaryotes. J Mol Evol. 30(5):449–455.

Daley JM, Sung P. 2014. 53BP1, BRCA1, and the choice between recombination and end joining at DNA double-strand rreaks. Mol Cell Biol. 34(8):1380–1388.

Deal RB, Henikoff S. 2011. The INTACT method for cell type-specific gene expression and chromatin profiling in *Arabidopsis thaliana*. Nat Protoc. 6(1):56–68.

Dong F, Song Z, Yu J, Zhang B, Jiang B, Shen Y, Lu Y, Song C, Cong P, Liu H. 2016. Dynamic changes in occupancy of histone variant H2A.Z during induced somatic cell reprogramming. Stem Cells Int. 2016:3162363.

Dong Q, Wang Y, Qi S, Gai K, He Q, Wang Y. 2018. Histone variant H2A.Z antagonizes the positive effect of the transcriptional activator CPC1 to regulate catalase-3 expression under normal and oxidative stress conditions. Free Radic Biol Med. 121:136–148.

Downs JA, Allard S, Jobin-Robitaille O, Javaheri A, Auger A, Bouchard N, Kron SJ, Jackson SP, Côté J. 2004. Binding of chromatin-modifying activities to phosphorylated histone H2A at DNA damage sites. Mol Cell. 16(6):979–990.

Doyon Y, Côté J. 2004. The highly conserved and multifunctional NuA4 HAT complex. Curr Opin Genet Dev. 14(2): 147–154.

Draker R, Sarcinella E, Cheung P. 2011. USP10 deubiquitylates the histone variant H2A.Z and both are required for androgen receptor-mediated gene activation. Nucleic Acids Res. 39(9):3529–3542.

Eddy SR. 2009. A new generation of homology search tools based on probabilistic inference. Genome Inform. 23(1): 205–211.

Ehinger A, Denison SH, May GS. 1990. Sequence, organization and expression of the core histone genes of *Aspergillus nidulans*. Mol Gen Genet. 222(2–3):416–424.

Eissenberg JC, Wong M, Chrivia JC. 2005. Human SRCAP and Drosophila Melanogaster DOM are homologs that function in the notch signaling pathway. Mol Cell Biol. 25(15): 6559–6569.

Faast R, Thonglairoam V, Schulz TC, Beall J, Wells JR, Taylor H, Matthaei K, Rathjen PD, Tremethick DJ, Lyons I. 2001. Histone variant H2A.Z is required for early mammalian development. Curr Biol. 11(15):1183–1187.

Freitag M, Hickey PC, Khlafallah TK, Read ND, Selker EU. 2004. HP1 is essential for DNA methylation in neurospora. Mol Cell. 13(3):427–434.

Gerhold CB, Gasser SM. 2014. INO80 and SWR complexes: relating structure to function in chromatin remodeling. Trends Cell Biol. 24(11):619–631.

Giaimo BD, Ferrante F, Herchenröther A, Hake SB, Borggrefe T. 2019. The histone variant H2A.Z in gene regulation. Epigenet Chromatin. 12(1):37.

Goswami RS, Kistler HC. 2004. Heading for disaster: *Fusarium graminearum* on cereal crops. Mol Plant Pathol. 5(6): 515–525.

Grabarz A, Guirouilh-Barbat J, Barascu A, Pennarun G, Genet D, Rass E, Germann SM, Bertrand P, Hickson ID, Lopez BS. 2013. A role for BLM in double-strand break repair pathway choice: prevention of CtIP/Mre11-mediated alternative nonhomologous end-joining. Cell Rep. 5(1):21–28.

Gruber-Dorninger C, Jenkins T, Schatzmayr G. 2019. Global mycotoxin occurrence in feed: a ten-year survey. Toxins. 11(7):375.

Gu Q, Ji T, Sun X, Huang H, Zhang H, Lu X, Wu L, Huo R, Wu H, Gao X. 2017. Histone H3 Lysine 9 methyltransferase FvDim5 regulates fungal development, pathogenicity and osmotic stress responses in Fusarium Verticillioides. FEMS Microbiol Lett. 364(19).DOI:10.1093/femsle/fnx184

Guillemette B, Gaudreau L. 2006. H2A.Z: a histone variant that decorates gene promoters. Med Sci (Paris). 22(11): 941–946.

Guindon S, Dufayard J-F, Lefort V, Anisimova M, Hordijk W, Gascuel O. 2010. New algorithms and methods to estimate maximum-likelihood phylogenies: assessing the performance of PhyML 3.0. Syst Biol. 59(3):307–321.

Gursoy-Yuzugullu O, Ayrapetov MK, Price BD. 2015. Histone chaperone Anp32e removes H2A.Z from DNA double-strand breaks and promotes nucleosome reorganization and DNA repair. Proc Natl Acad Sci USA. 112(24): 7507–7512.

Hartley PD, Madhani HD. 2009. Mechanisms that specify promoter nucleosome location and identity. Cell. 137(3): 445–458.

Hatakeyama S, Ishii C, Inoue H. 1995. Identification and expression of the *Neurospora crassa* Mei-3 gene which encodes a protein homologous to Rad51 of *Saccharomyces cerevisiae*. Mol Gen Genet. 249(4):439–446.

Hawksworth D, Lücking R. 2017. Fungal diversity revisited: 2.2 to 3.8 million species. In: Heitman J, Howlett B, Crous P, Stukenbrock E, James T, Gow N, editors. The Fungal Kingdom. Washington, DC: ASM Press. p. 79–95. DOI:10.1128/microbiolspec.FUNK-0052-2016

Hays SM, Swanson J, Selker EU. 2002. Identification and characterization of the genes encoding the core histones and histone variants of *Neurospora crassa*. Genetics. 160(3): 961–973.

Hiom K. 2010. Coping with DNA double strand breaks. DNA Repair (Amst). 9(12):1256–1263.

Hu G, Cui K, Northrup D, Liu C, Wang C, Tang Q, Ge K, Levens D, Crane-Robinson C, Zhao K. 2013. H2A.Z facilitates access of active and repressive complexes to

chromatin in embryonic stem cell self-renewal and differentiation. Cell Stem Cell. 12(2):180–192.
Hu Y, Shen Y, Conde e Silva N, Zhou D-X. 2011. The role of histone methylation and H2A.Z occupancy during rapid activation of ethylene responsive genes. PLoS One. 6(11): e28224.
Hussein HS, Brasel JM. 2001. Toxicity, metabolism, and impact of mycotoxins on humans and animals. Toxicology. 167(2):101–134.
Ikura T, Ogryzko VV, Grigoriev M, Groisman R, Wang J, Horikoshi M, Scully R, Qin J, Nakatani Y. 2000. Involvement of the TIP60 histone acetylase complex in DNA repair and apoptosis. Cell. 102(4):463–473.
Ishibashi K, Suzuki K, Ando Y, Takakura C, Inoue H. 2006. Nonhomologous chromosomal integration of foreign DNA is completely dependent on MUS-53 (Human Lig4 Homolog) in neurospora. Proc Natl Acad Sci USA. 103(40): 14871–14876.
Jackson JD, Falciano VT, Gorovsky MA. 1996. A likely histone H2A.F/Z variant in *Saccharomyces cerevisiae*. Trends Biochem Sci. 21(12):466–467.
Jackson JD, Gorovsky MA. 2000. Histone H2A.Z has a conserved function that is distinct from that of the major H2A sequence variants. Nucleic Acids Res. 28(19):3811–3816.
Jin J, Cai Y, Yao T, Gottschalk AJ, Florens L, Swanson SK, Gutiérrez JL, Coleman MK, Workman JL, Mushegian A, et al. 2005. A mammalian chromatin remodeling complex with similarities to the yeast INO80 complex. J Biol Chem. 280(50):41207–41212.
Jin C, Felsenfeld G. 2007. Nucleosome stability mediated by histone variants H3.3 and H2A.Z. Genes Dev. 21(12): 1519–1529.
Kalocsay M, Hiller NJ, Jentsch S. 2009. Chromosome-wide Rad51 spreading and SUMO-H2A.Z-dependent chromosome fixation in response to a persistent DNA double-strand break. Mol Cell. 33(3):335–343.
Katoh H, Ohtani K, Yamamoto H, Akimitsu K. 2007. Overexpression of a gene encoding a catabolite repression element in *Alternaria citri* causes severe symptoms of black rot in citrus fruit. Phytopathology. 97(5):557–563.
Keogh M-C, Mennella TA, Sawa C, Berthelet S, Krogan NJ, Wolek A, Podolny V, Carpenter LR, Greenblatt JF, Baetz K, et al. 2006. The *Saccharomyces cerevisiae* histone H2A variant Htz1 is acetylated by NuA4. Genes Dev. 20(6):660–665.
Kim JS, JT, Heale W, Zeng X, Kong TB, Krasieva AR, Ball K. Yokomori 2007. In situ analysis of DNA damage response and repair using laser microirradiation. Methods Cell Biol. 82:377–407.
Kobor MS, Venkatasubrahmanyam S, Meneghini MD, Gin JW, Jennings JL, Link AJ, Madhani HD, Rine J. 2004. A protein complex containing the conserved Swi2/Snf2-related ATPase Swr1p deposits histone variant H2A.Z into euchromatin. PLoS Biol. 2(5):E131.
Kornberg RD. 1999. Eukaryotic transcriptional control. Trends Cell Biol. 9(12):M46–M49.
Kornberg RD. 2007. The molecular basis of eukaryotic transcription. Proc Natl Acad Sci USA. 104(32):12955–12961.
Krogan NJ, Keogh M-C, Datta N, Sawa C, Ryan OW, Ding H, Haw RA, Pootoolal J, Tong A, Canadien V, et al. 2003. A Snf2 family ATPase complex required for recruitment of the histone H2A variant Htz1. Mol Cell. 12(6):1565–1576.
Krogan NJ, Peng W-T, Cagney G, Robinson MD, Haw R, Zhong G, Guo X, Zhang X, Canadien V, Richards DP, et al. 2004. High-definition macromolecular composition of yeast RNA-processing complexes. Mol Cell. 13(2):225–239.
Ku M, Jaffe JD, Koche RP, Rheinbay E, Endoh M, Koseki H, Carr SA, Bernstein BE. 2012. H2A.Z landscapes and dual modifications in pluripotent and multipotent stem cells underlie complex genome regulatory functions. Genome Biol. 13(10):R85.
Kurat CF, Recht J, Radovani E, Durbic T, Andrews B, Fillingham J. 2014. Regulation of histone gene transcription in yeast. Cell Mol Life Sci. 71(4):599–613.
Kusch T, Florens L, Macdonald WH, Swanson SK, Glaser RL, Yates JR, Abmayr SM, Washburn MP, Workman JL. 2004. Acetylation by Tip60 is required for selective histone variant exchange at DNA lesions. Science. 306(5704): 2084–2087.
Leach TJ, Mazzeo M, Chotkowski HL, Madigan JP, Wotring MG, Glaser RL. 2000. Histone H2A.Z is widely but nonrandomly distributed in chromosomes of Drosophila Melanogaster. J Biol Chem. 275(30):23267–23272.
Letunic I, Bork P. 2018. 20 Years of the SMART protein domain annotation resource. Nucleic Acids Res. 46(D1): D493–D496.
Letunic I, Doerks T, Bork P. 2015. SMART: recent updates, new developments and status in 2015. Nucleic Acids Res. 43(Database issue):D257–D260.
Liu X, Li B, Null Gorovsky MA. 1996. Essential and nonessential histone H2A ariants in *Tetrahymena thermophila*. Mol Cell Biol. 16(8):4305–4311.
Liu Y, Liu N, Yin Y, Chen Y, Jiang J, Ma Z. 2015. Histone H3K4 methylation regulates hyphal growth, secondary metabolism and multiple stress responses in *Fusarium graminearum*. Environ Microbiol. 17(11):4615–4630.
Luger K, Dechassa ML, Tremethick DJ. 2012. New insights into nucleosome and chromatin structure: an ordered state or a disordered affair? Nat Rev Mol Cell Biol. 13(7): 436–447.
Luger K, Mäder AW, Richmond RK, Sargent DF, Richmond TJ. 1997. Crystal structure of the nucleosome core particle at 2.8 A resolution. Nature. 389(6648):251–260.
Lusser A, Kadonaga JT. 2003. Chromatin remodeling by ATP-dependent molecular machines. Bioessays. 25(12): 1192–1200.
Mao P, Meas R, Dorgan KM, Smerdon MJ. 2014. UV damage-induced RNA polymerase II stalling stimulates H2B deubiquitylation. Proc Natl Acad Sci USA. 111(35):12811–12816.
March-Díaz R, Reyes JC. 2009. The beauty of being a variant: H2A.Z and the SWR1 complex in plants. Mol Plant. 2(4): 565–577.
Mariño-Ramírez L, Kann MG, Shoemaker BA, Landsman D. 2005. Histone structure and nucleosome stability. Expert Rev Proteomics. 2(5):719–729.
Marques JT, Kim K, Wu P-H, Alleyne TM, Jafari N, Carthew RW. 2010. Loqs and R2D2 act sequentially in the SiRNA pathway in Drosophila. Nat Struct Mol Biol. 17(1):24–30.
Marzluff WF, Koreski KP. 2017. Birth and death of histone MRNAs. Trends Genet. 33(10):745–759.
Mavrich TN, Jiang C, Ioshikhes IP, Li X, Venters BJ, Zanton SJ, Tomsho LP, Qi J, Glaser RL, Schuster SC, et al. 2008. Nucleosome organization in the *Drosophila* genome. Nature. 453(7193):358–362.

May GS, Morris NR. 1987. The unique histone H2A gene of *Aspergillus nidulans* contains three introns. Gene. 58(1): 59–66.

Maze I, Noh K-M, Soshnev AA, Allis CD. 2014. Every amino acid matters: essential contributions of histone variants to mammalian development and disease. Nat Rev Genet. 15(4):259–271.

Mizuguchi G, Shen X, Landry J, Wu W-H, Sen S, Wu C. 2004. ATP-driven exchange of histone H2AZ variant catalyzed by SWR1 chromatin remodeling complex. Science. 303(5656): 343–348.

Morrison AJ, Shen X. 2009. Chromatin remodelling beyond transcription: the INO80 and SWR1 complexes. Nat Rev Mol Cell Biol. 10(6):373–384.

Nielsen ML, Albertsen L, Lettier G, Nielsen JB, Mortensen UH. 2006. Efficient PCR-based gene targeting with a recyclable marker for *Aspergillus nidulans*. Fungal Genet Biol. 43(1): 54–64.

Nielsen JB, Nielsen ML, Mortensen UH. 2008. Transient disruption of non-homologous end-joining facilitates targeted genome manipulations in the filamentous fungus *Aspergillus nidulans*. Fungal Genet Biol. 45(3):165–170.

Ninomiya Y, Suzuki K, Ishii C, Inoue H. 2004. Highly efficient gene replacements in neurospora strains deficient for non-homologous end-joining. Proc Natl Acad Sci USA. 101(33): 12248–12253.

Nishida H, Yun C-S. 2011. Extraction of tentative mobile introns in fungal histone genes. Mob Genet Elements. 1(1): 78–79.

Obri A, Ouararhni K, Papin C, Diebold M-L, Padmanabhan K, Marek M, Stoll I, Roy L, Reilly PT, Mak TW, et al. 2014. ANP32E is a histone chaperone that removes H2A.Z from chromatin. Nature. 505(7485):648–653.

Park Y-J, Dyer PN, Tremethick DJ, Luger K. 2004. A new fluorescence resonance energy transfer approach demonstrates that the histone variant H2AZ stabilizes the histone octamer within the nucleosome. J Biol Chem. 279(23): 24274–24282.

Peserico A, Simone C. 2011. Physical and functional HAT/HDAC interplay regulates protein acetylation balance. J Biomed Biotechnol. 2011:371832.

Pfannenstiel BT, Keller NP. 2019. On top of biosynthetic gene clusters: how epigenetic machinery influences secondary metabolism in fungi. Biotechnol. Adv. 37(6):107345.

Prigione V, Spina F, Tigini V, Giovando S, Varese GC. 2018. Biotransformation of industrial tannins by filamentous fungi. Appl Microbiol Biotechnol. 102(24):10361–10375.

Raisner RM, Hartley PD, Meneghini MD, Bao MZ, Liu CL, Schreiber SL, Rando OJ, Madhani HD. 2005. Histone variant H2A.Z marks the 5′ ends of both active and inactive genes in euchromatin. Cell. 123(2):233–248.

Reyes-Dominguez Y, Boedi S, Sulyok M, Wiesenberger G, Stoppacher N, Krska R, Strauss J. 2012. Heterochromatin influences the secondary metabolite profile in the plant pathogen *Fusarium graminearum*. Fungal Genet Biol. 49(1): 39–47.

Richmond TJ, Finch JT, Rushton B, Rhodes D, Klug A. 1984. Structure of the nucleosome core particle at 7 A resolution. Nature. 311(5986):532–537.

Rispal J, Baron L, Beaulieu J-F, Chevillard-Briet M, Trouche D, Escaffit F. 2019. The H2A.Z histone variant integrates Wnt signaling in intestinal epithelial homeostasis. Nat Commun. 10(1):1–14.

Robert X, Gouet P. 2014. Deciphering key features in protein structures with the new ENDscript server. Nucleic Acids Res. 42(Web Server issue):W320–W324.

Ruhl DD, Jin J, Cai Y, Swanson S, Florens L, Washburn MP, Conaway RC, Conaway JW, Chrivia JC. 2006. Purification of a human SRCAP complex that remodels chromatin by incorporating the histone variant H2A.Z into nucleosomes. Biochemistry. 45(17):5671–5677.

Ryan DP, Owen-Hughes T. 2011. Snf2-family proteins: chromatin remodellers for any occasion. Curr Opin Chem Biol. 15(5):649–656.

Ryan DP, Tremethick DJ. 2018. The interplay between H2A.Z and H3K9 methylation in regulating HP1α binding to linker histone-containing chromatin. Nucleic Acids Res. 46(18):9353–9366.

Sadeghi L, Bonilla C, Strålfors A, Ekwall K, Peter Svensson J. 2011. Podbat: a novel genomic tool reveals Swr1-independent H2A.Z incorporation at gene coding sequences through epigenetic meta-analysis. PLoS Comput Biol. 7(8): e1002163.

Santisteban MS, Hang M, Mitchell Smith M. 2011. Histone variant H2A.Z and RNA polymerase II transcription elongation. Mol Cell Biol. 31(9):1848–1860.

Santos-Rosa H, Schneider R, Bannister AJ, Sherriff J, Bernstein BE, Tolga Emre NC, Schreiber SL, Mellor J, Kouzarides T. 2002. Active genes are tri-methylated at K4 of histone H3. Nature. 419(6905):407–411.

Sarcinella E, Zuzarte PC, Lau PNI, Draker R, Cheung P. 2007. Monoubiquitylation of H2A.Z distinguishes its association with euchromatin or facultative heterochromatin. Mol Cell Biol. 27(18):6457–6468.

Sarrocco S, Mauro A, Battilani P. 2019. Use of competitive filamentous fungi as an alternative approach for mycotoxin risk reduction in staple cereals: state of art and future perspectives. Toxins. 11(12):701.

Sartori AA, Lukas C, Coates J, Mistrik M, Fu S, Bartek J, Baer R, Lukas J, Jackson SP. 2007. Human CtIP promotes DNA end resection. Nature. 450(7169):509–514.

Sevilla A, Binda O. 2014. Post-translational modifications of the histone variant H2az. Stem Cell Res. 12(1):289–295.

Sims RJ, Mandal SS, Reinberg D. 2004. Recent highlights of RNA-polymerase-II-mediated transcription. Curr Opin Cell Biol. 16(3):263–271.

Smith ER, Eisen A, Gu W, Sattah M, Pannuti A, Zhou J, Cook RG, Lucchesi JC, Allis CD. 1998. ESA1 is a histone acetyltransferase that is essential for growth in yeast. Proc Natl Acad Sci USA. 95(7):3561–3565.

Smith CL, Peterson CL. 2005. ATP-dependent chromatin remodeling. Curr Top Dev Biol. 65:115–148.

Soboleva TA, Nekrasov M, Ryan DP, Tremethick DJ. 2014. Histone variants at the transcription start-site. Trends Genet. 30(5):199–209.

Strauss J, Reyes-Dominguez Y. 2011. Regulation of secondary metabolism by chromatin structure and epigenetic codes. Fungal Genet Biol. 48(1):62–69.

"Stop Neglecting Fungi." 2017. Nat Microbiol. 2(8):17120.

Studt L, Rösler SM, Burkhardt I, Arndt B, Freitag M, Humpf H-U, Dickschat JS, Tudzynski B. 2016. Knock-down of the methyltransferase Kmt6 relieves H3K27me3 and results in induction of cryptic and otherwise silent secondary

metabolite gene clusters in *Fusarium fujikuroi*. Environ Microbiol. 18(11):4037–4054.
Subramanian V, Fields PA, Boyer LA. 2015. H2A.Z: a molecular rheostat for transcriptional control. F1000Prime Rep. 7:1.
Sura W, Kabza M, Karlowski WM, Bieluszewski T, Kus-Slowinska M, Pawełoszek Ł, Sadowski J, Ziolkowski PA. 2017. Dual role of the histone variant H2A.Z in transcriptional regulation of stress-response genes. Plant Cell. 29(4):791–807.
Suto RK, Clarkson MJ, Tremethick DJ, Luger K. 2000. Crystal structure of a nucleosome core particle containing the variant histone H2A.Z. Nat Struct Biol. 7(12):1121–1124.
Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, Simonovic M, Doncheva NT, Morris JH, Bork P, et al. 2019. STRING V11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 47(D1):D607–D613.
Talbert PB, Henikoff S. 2010. Histone variants-ancient wrap artists of the epigenome. Nat Rev Mol Cell Biol. 11(4): 264–275.
Talbert PB, Henikoff S. 2014. Environmental responses mediated by histone variants. Trends Cell Biol. 24(11):642–650.
Talbert PB, Henikoff S. 2017. Histone variants on the move: substrates for chromatin dynamics. Nat Rev Mol Cell Biol. 18(2):115–126.
Taty-Taty G-C, Courilleau C, Quaranta M, Carayon A, Chailleux C, Aymard F, Trouche D, Canitrot Y. 2014. H2A.Z depletion impairs proliferation and viability but not DNA double-strand breaks repair in human immortalized and tumoral cell lines. Cell Cycle. 13(3):399–407.
Thambirajah AA, Dryhurst D, Ishibashi T, Li A, Maffey AH, Ausió J. 2006. H2A.Z stabilizes chromatin in a way that is dependent on core histone acetylation. J Biol Chem. 281(29):20036–20044.
Thatcher TH, Gorovsky MA. 1994. Phylogenetic analysis of the core histones H2A, H2B, H3, and H4. Nucleic Acids Res. 22(2):174–179.
Tisch D, Schmoll M. 2010. Light regulation of metabolic pathways in fungi. Appl Microbiol Biotechnol. 85(5):1259–1277.
Tosi A, Haas C, Herzog F, Gilmozzi A, Berninghausen O, Ungewickell C, Gerhold CB, Lakomek K, Aebersold R, Beckmann R, et al. 2013. Structure and subunit topology of the INO80 chromatin remodeler and its nucleosome complex. Cell. 154(6):1207–1219.
Valdés-Mora F, Song JZ, Statham AL, Strbenac D, Robinson MD, Nair SS, Patterson KI, Tremethick DJ, Stirzaker C, Clark SJ. 2012. Acetylation of H2A.Z is a key epigenetic modification associated with gene deregulation and epigenetic remodeling in cancer. Genome Res. 22(2):307–321.
Vogler C, Huber C, Waldmann T, Ettig R, Braun L, Izzo A, Daujat S, Chassignet I, Lopez-Contreras AJ, Fernandez-Capetillo O, et al. 2010. Histone H2A C-terminus regulates chromatin dynamics, remodeling, and histone H1 binding. PLoS Genet. 6(12):e1001234.
Weber CM, Ramachandran S, Henikoff S. 2014. Nucleosomes are context-specific, H2A.Z-modulated barriers to RNA polymerase. Mol Cell. 53(5):819–830.
White JH, DiMartino JF, Anderson RW, Lusnak K, Hilbert D, Fogel S. 1988. A DNA sequence conferring high postmeiotic segregation frequency to heterozygous deletions in *Saccharomyces cerevisiae* is related to sequences associated with eucaryotic recombination hotspots. Mol Cell Biol. 8(3):1253–1258.
Wong KH, Hynes MJ, Davis MA. 2008. Recent advances in nitrogen regulation: a comparison between *Saccharomyces cerevisiae* and filamentous fungi. Eukaryotic Cell. 7(6): 917–925.
Wong J, Nakajima Y, Westermann S, Shang C, Kang J-S, Goodner C, Houshmand P, Fields S, Chan CSM, Drubin D, et al. 2007. A protein interaction map of the mitotic spindle. Mol Biol Cell. 18(10):3800–3809.
Wösten HAB. 2019. Filamentous fungi for the production of enzymes, chemicals and materials. Curr Opin Biotechnol. 59:65–70.
Wratting D, Thistlethwaite A, Harris M, Zeef LAH, Millar CB. 2012. A conserved function for the H2A.Z C terminus. J Biol Chem. 287(23):19148–19157.
Xu Y, Ayrapetov MK, Xu C, Gursoy-Yuzugullu O, Hu Y, Price BD. 2012. Histone H2A.Z controls a critical chromatin remodeling step required for DNA double-strand break repair. Mol Cell. 48(5):723–733.
Zhang C, Cao L, Rong L, An Z, Zhou W, Ma J, Shen W-H, Zhu Y, Dong A. 2015. The chromatin-remodeling factor AtINO80 plays crucial roles in genome stability maintenance and in plant development. Plant J. 82(4):655–668.
Zhang H, Roberts DN, Cairns BR. 2005. Genome-wide dynamics of Htz1, a histone H2A variant that poises repressed/basal promoters for activation through histone loss. Cell. 123(2):219–231.
Zhao H, Lovett B, Fang W. 2016. Genetically engineering entomopathogenic fungi. Adv Genet. 94:137–163.
Zilberman D, Coleman-Derr D, Ballinger T, Henikoff S. 2008. Histone H2A.Z and DNA methylation are mutually antagonistic chromatin marks. Nature. 456(7218):125–129.