Histone variant H2A.Z promotes meiotic chromosome axis organization in Saccharomyces cerevisiae

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Abstract
Progression through meiosis is associated with significant reorganization of chromosome structure, regulated in part by changes in histones and chromatin. Prior studies observed defects in meiotic progression in yeast strains lacking the linker histone H1 or variant histone H2A.Z. To further define the contributions of these chromatin factors, we have conducted genetic and cytological analysis of cells undergoing meiosis in the absence of H1 and H2A.Z. We find that a spore viability defect observed in strains lacking H2A.Z can be partially suppressed if cells also lack histone H1, while the combined loss of both H1 and H2A.Z is associated with elevated gene conversion events. Cytological analysis of Red1 and Rec8 staining patterns indicates that a subset of cells lacking H2A.Z fail to assemble a proper chromosome axis, and the staining pattern of the synaptonemal complex protein Zip1 in htz1Δ/htz1Δ cells mimics that of cells deficient for Rec8-dependent meiotic cohesion. Our results suggest a role for H2A.Z in the establishment or maintenance of the meiotic chromosome axis, possibly by promoting the efficient chromosome cohesion.

Keywords: meiosis; chromatin; histone H1; H2A.Z

Introduction
Meiosis is a specialized cellular differentiation program allowing diploid cells to follow a single cycle of DNA replication with 2 successive cell divisions, resulting in the generation of 4 haploid cells. In yeast and other organisms, meiosis is associated with changes in the structure of chromatin that influence the execution of a unique gene expression program, the creation and repair of DNA double-strand breaks, and the regulation of chromosome pairing and segregation patterns specific to meiosis (Govin and Berger 2009; Neiman 2011; Hunter 2015; Jaiswal et al. 2017); Hong et al. 2019). In yeast cells, sporulation is not associated with widespread changes in genome-wide nucleosome occupancy or positioning (Zhang et al. 2011), but progression through meiosis is correlated with specific alterations in the posttranslational modification of histones (Krishnamoorthy et al. 2006; Govin, Dorsey, et al. 2010; Govin, Schug, et al. 2010; Hu et al. 2015; Kniewel et al. 2017; reviewed in Govin and Berger 2009; Jaiswal et al. 2017; Wang et al. 2017). Meiosis is also influenced by the presence of linker histone H1 and the variant histone H2A.Z. Histone H1 is encoded by the HHO1 gene in budding yeast, and its absence in vegetative cells is associated with relatively subtle phenotypes (Patterson et al. 1998; Downs et al. 2003; Veron et al. 2006; Li et al. 2008; Kowalski and Palyga 2012; Lawrence et al. 2017). In yeast cells, diploids lacking H1 are reported to have mild defects in sporulation efficiency (Bryant et al. 2012) with sporule viability and recombination efficiencies similar to those of wild-type cells (Bryant et al. 2012; Brush 2015). H1 may partner with the Ume6 repressor to limit the expression of early meiotic genes during vegetative growth, while enrichment of H1 during spore maturation may contribute to chromatin compaction (Bryant et al. 2012).

H2A.Z, encoded by the HTZ1 gene in budding yeast, is a highly conserved variant of the canonical histone H2A; yeast cells lacking H2A.Z have a variety of defects in gene expression, DNA damage repair, and chromosome segregation (Santisteban et al. 2000; Meneghini et al. 2003; Krogan et al. 2004; Kalocsay et al. 2009; reviewed in Billon and Cote 2013; Giaimo et al. 2019). Fission yeast lacking H2A.Z are deficient in the formation of the double-strand DNA breaks that initiate meiotic recombination (Yamada et al. 2018), yet increases the frequency of crossovers at some loci (Yamada et al. 2020). No such defect in DNA break formation was observed in budding yeast cells lacking H2A.Z (Gonzalez-Arranz et al. 2018); however, htz1Δ/htz1Δ diploids were observed to show reduced sporulation efficiency and spore viability, had defects in resumption of progression through meiosis following activation of the meiotic recombination checkpoint, and exhibited reduced chromosome movement in meiotic prophase (Gonzalez-Arranz et al. 2018, 2020).

Successful meiosis depends on formation of a specialized chromosome axis that includes the Red1 and Hop1 proteins, and the meiosis-specific cohesin Rec8 (Hollingsworth et al. 1990; Smith and Roeder 1997; Klein et al. 1999; Zickler and Kleckner 1999). This axis is required for the subsequent assembly of the synaptonemal complex (SC), which facilitates the intimate association of homologous chromosomes and regulates the interhomolog recombination events that are essential for proper...
chromosome segregation at meiosis I (Page and Hawley 2003). The varied meiotic defects observed in yeast cells lacking either H1 or H2A.Z could stem from defects in the formation of chromosomal axes or the downstream process of SC assembly. In this study, we examined the individual and joint contributions of H1 and H2A.Z to meiotic prophase chromosomal events. Our study extends prior work indicating that loss of H1 or H2A.Z does not alter patterns of recombination during meiosis, demonstrates that loss of H1 can suppress the decrease in spore viability caused by the absence of H2A.Z, and identifies a chromosome axis defect in cells lacking H2A.Z. Our results suggest that in a subset of meiotic cells, H2A.Z plays a key role in establishing or stabilizing chromosome axes.

**Materials and methods**

**Strains**

All Saccharomyces cerevisiae strains used in this study are isogenic to BR1919-B8 (Rockmill and Roeder 1998) and are described in Table 1. Strain YSH1496 was created by crossing haploid strains YSH1305 (MATa) and YSH1306 (MATa). Gene deletions in each haploid were performed via standard PCR-based gene disruptions (Wach et al. 1994) using MX plasmids as templates (Goldstein and McCusker 1999; Knop et al. 1999); haploids were then mated to create homozygous diploids. Diploids deleted for both HTZ1 and HHO1 were created by standard crosses and tetrad dissections. Strains YSH1496 (wild type), YSH1497 (htz1A/htz1A), YSH1498 (hto1A/hho1A), and YSH1515 (htz1A/htz1A hho1A/hho1A) were used for spore viability, sporulation efficiency, and recombination assays. These strains are heterozygous for markers on chromosomes III and VIII to facilitate recombination analysis, as illustrated in Fig. 2a (Voelkel-Meiman et al. 2016).

Diploids were induced to undergo meiosis on solid sporulation media (0.1% yeast extract and 1% potassium acetate) at 30°C for 5 days; cells were then assessed for sporulation efficiency, spore viability, and recombination efficiency as described (Voelkel-Meiman et al. 2016). Stahl Lab Online Tools (https://elizabethhousworth.com/StahlLabOnlineTools/) were used to calculate recombination efficiencies and crossover interference (Stahl and Lande 1995).

**Table 1. Strains.**

| Strain   | Genotype                                                                 |
|----------|--------------------------------------------------------------------------|
| BR1919   | MATa ura3-1 thr1-4 trp1-289 ade2-1 his4-260,519 leu2-3,112 lys2            |
| YSH1305  | MATa ura3-1 ade2-1 trp1-289 leu2-3,112 lys2ΔNhe hphMX4@CEN3 ADE2@RAD18 natMX4@HMR TRP1@SPO11 spo13A::URA3 HIS4 THR1 |
| YSH1306  | MATa ura3-1 thr1-4 trp1-289 ade2-1 his4-260,519 leu2-3,112 lys2ΔNhe LYS2@C8 (210Kb) |
| YSH1496  | MATa lys2ΔNhe leu2-3,11 ade2-1 ura3-1 trp1-289 thr1-4 LYS2@C8                |
|          | MATa lys2ΔNhe leu2-3,11 ade2-1 ura3-1 trp1-289 THR1 cVIII                  |
|          | his4-260,519 spo13A::URA3 HIS4 MX4@CEN3 TRP1@SPO11 natMX4@HMR             |
|          | HIS4                      | CEN3                      | SPO11                      | HMR                      |
| YSH1497  | YSH1496, htz1A::kanMX4/hhtz1A::kanMX4                                    |
| YSH1498  | YSH1496, hho1A::kanMX4/hho1A::kanMX4                                    |
| YSH1515  | YSH1496, htz1A::kanMX4/hhtz1A::kanMX4                                    |
| YSH1304  | MATa ura3-1 thr1-4 trp1-289 ade2-1 his4-260,519 leu2-3,112 lys2ΔNhe ndt80A::LEU2 |
| YSH1307  | MATa ura3-1 thr1-4 trp1-289 ade2-1 his4-260,519 leu2-3,112 lys2ΔNhe zip1A::hphMX4 ECM11-13MYC-kanMX4 ndt80A::LEU2 |
| YSH1524  | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2ΔNhe              |
|          | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2ΔNhe              |
|          | his4-260,519 ECM11 HTZ1 HHO1                                             |
|          | his4-260,519 ECM11 HTZ1 HHO1                                             |
| YSH1525  | YSH1504, htz1A::natMX4/hhtz1A::natMX4                                    |
| YSH1526  | YSH1504, hho1A::natMX4/hho1A::natMX4                                    |
| YSH1527  | YSH1504, htz1A::natMX4/hhtz1A::natMX4                                    |
| YSH1616  | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2                  |
|          | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2                  |
|          | his4-260,519 ura3-1 REC8 HTZ1 HHO1                                       |
|          | his4-260,519 ura3-1 REC8 HTZ1 HHO1                                       |
| YSH1618  | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2                  |
|          | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2                  |
|          | his4-260,519 ura3-1 REC8-MYC-kanMX4 HTZ1 HHO1                             |
|          | his4-260,519 ura3-1 REC8-MYC-kanMX4 HTZ1 HHO1                             |
| YSH1620  | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2                  |
|          | MATa trp1-289 leu2-3,112 ade2-1 thr1-4 ndt80A::LEU2 lys2                  |
|          | his4-260,519 ura3-1 REC8-MYC-kanMX4 htz1A::natMX4 HHO1                    |
|          | his4-260,519 ura3-1 REC8-MYC-kanMX4 htz1A::natMX4 HHO1                    |
Cytological analysis and imaging

Strains used for cytological analysis are homozygous ndt80A::LEU2; these diploids arrest at pachytene of prophase I. Diploid strains homozygous for specific gene deletions were created by first deleting the HTZ1 and HHO1 genes in haploid strains YSH1304 (MATa) and YSH1307 (MATa) followed by crosses. Strains YSH1524 (wild-type), YSH1525 (hzt1A/hzt1A), YSH1526 (hho1A/hho1A), and YSH1527 (hzt1A/hzt1A hho1A/hho1A) were used for cytological analysis. Diploids were induced to sporulate in liquid media at 30°C, and then, meiotic chromosomes were surface spread on glass slides as described (Rockmill 2009; Voelkel-Meiman et al. 2012). Spread chromosomes were immunostained as described (Voelkel-Meiman et al. 2019). Prior to imaging, 12 μL of glycerol-based mounting medium containing 1mg/mL DAPI was added to each slide; a cover slip was then placed on top of each slide. Imaging was performed using the DeltaVision RT imaging system (General Electric) adapted to an Olympus (IX71) microscope. Antibodies targeting SC transverse filament protein Zip1 and targeting the SC central element protein(s) Ecm11-Gmc2 (Voelkel-Meiman et al. 2019) were used to assess the SC structure. Random nuclei for each genotype were analyzed for their Zip1 and Ecm11-Gmc2 staining pattern and placed into one of 4 categories: linear (fully continuous lines of Zip1); dotty linear (mixture of Zip1 foci and short linear stretches); and dotty (foci only) (Voelkel-Meiman et al. 2012). Nuclei with a fuzzy/misty Zip1 pattern that is coincident with DAPI staining were placed into the “diffuse” category.

Results

Cells lacking H2A.Z have decreased spore viability

To assess the influence of histones H2A.Z and H1 on meiosis in budding yeast, we measured sporulation efficiency, spore viability, and recombination in diploid strains lacking HHO1, HTZ1, or both (Table 2). We measured the sporulation efficiency by calculating the percentage of diploids that formed spores (either dyads, triads, or tetrads) when cells were plated in media that induce sporulation. Wild-type diploids sporulated at 50% efficiency, similar to prior reports using this strain background (Rockmill and Roeder 1990). Previous studies indicated modest decreases in sporulation efficiency for diploids lacking H2A.Z (Gonzalez-Arranz et al. 2018) or H1 (Bryant et al. 2012), in our experiments, we observed sporulation efficiencies equivalent to wild-type cells in strains missing H2A.Z, H1, or both (Fig. 1a and Table 2).

Spore viability is expressed as the number of spores that germinate and grow into a colony divided by the total number of spores examined. Wild-type diploids show high spore viability (96%; Fig. 1b and Table 2), similar to previously published values (Sym et al. 1993). The spore viability of hho1A/hho1A diploids is similar to that of the wild-type strain (94%), consistent with prior reports (Bryant et al. 2012; Brush 2015). We observed that deleting HTZ1 significantly reduced spore viability (73%), in agreement with a prior study (Gonzalez-Arranz et al. 2018). Interestingly, deleting HHO1 in the hzt1A strain caused a statistically significant improvement in spore viability (from 73% to 81%, P = 0.0006).

In strains lacking H2A.Z, only 40% of the tetrads contained 4 viable spores, vs >83% in wild-type cells or in cells lacking HHO1 (Fig. 1c and Table 2). H2A.Z promotes chromosome stability during vegetative growth (Krogan et al. 2004; Keogh et al. 2006; Sharma et al. 2013), and reduced spore viability is often a sign of defective chromosome segregation during either the meiosis I or meiosis II division. To investigate whether the reduced spore viability defect in the hzt1A strain is due to chromosome missegregation during the first meiotic division, we measured the rate of chromosome III nondisjunction events in MI. Nondisjunction of any single chromosome during meiosis I could lead to tetrads with 2 viable spores; if chromosome III undergoes nondisjunction at meiosis I and a normal meiosis II chromosome segregation pat-tern follows, then each of the 2 viable spore products will express both MATa and MATa and thus exhibit a nonmating phenotype. The percentage of 2-spore viable tetrads was elevated in the hzt1A mutants relative to wild type (13% vs 2.6%), but the incidence of nondisrupting 2-spore viable tetrads was not different between the 2 strains (Table 2). Thus, we fail to find the evidence of chromosome III nondisjunction during the first meiotic division.

The large increase in 3-spore viable tetrads we observed in the hzt1A mutants (32% in hzt1A vs 11% in wild type) suggests instead that chromatid nondisjunction events during the second meiotic division as a result of precocious sister chromatid separation may be the basis for the decreased spore viability of hzt1A mutants (Rockmill et al. 2006; Chu and Burgess 2016).

Histones H2A.Z and H1 are not required for efficient meiotic recombination

Meiotic recombination is initiated by the induction of programmed double-strand breaks that are repaired via homologous recombination. To determine if H2A.Z and H1 influence meiotic recombination, we measured recombination frequency across 7 intervals located on chromosomes III and VIII (Fig. 2a) using linkage analysis in strains carrying heterozygous alleles at 9 genetic loci. Our results for the wild-type strain closely match published values (Fig. 2b; Voelkel-Meiman et al. 2016). Consistent with a prior study assessing 4 intervals on chromosome XV (Brush 2015), we observe no significant changes in recombination rates on chromosomes III or VIII in cells lacking histone H1. Similarly, we observed no significant change in recombination on chromosome VIII due to the loss of H2A.Z, consistent with a prior report examining a single interval on chromosome VIII (Gonzalez-Arranz et al. 2018). However, we observed mildly elevated recombination over individual genetic intervals on chromosome III in the absence of H2A.Z (Fig. 2b and Table 3), and cumulatively, we observed that recombination on chromosome III was significantly elevated in both the hzt1A and hzt1A hho1A strains (Fig. 2c and Table 3). In wild-type cells, the presence of a crossover decreases the incidence of nearby crossovers (reviewed in Otto and Payseur 2019; von Diezmann and Rog 2021). We found that the individual or combined absence of H2A.Z and H1 did not significantly increase or decrease crossover interference (Table 3).

Meiotic gene conversion results in the non-Mendelian segregation of genetic markers, detectable by observing non-2:2 segregation patterns for heterozygous markers in 4-spore viable tetrads. We observed that the frequency of tetrads experiencing at least 1 gene conversion event is slightly elevated in strains lacking HHO1 or HTZ1, and more markedly in strains lacking both genes (Fig. 3 and Table 4). In addition, we observed an increase in the overall rate of gene conversions per tetrad of 1.3-times in the hho1A strain and 2.9-times in the hho1A hzt1A double mutant. Interestingly, this increase is almost exclusively due to increased gene conversion of chromosome III markers (Table 4; Supplementary Table 2 shows the frequency of gene conversion
Table 2. Sporulation efficiency and viability, nondisjunction frequency.

| Genotype       | Sporulation efficiency % (n) [P-value] | % spore viability | # total tetrads analyzed | # 4—Sporulation tetrads | # 3—Sporulation tetrads | # 2—Sporulation tetrads | # 1—Sporulation tetrads | # 0—Sporulation tetrads | Chromosome III nondisjunction (NDJ) % | # NDJ/#2 spore viable |
|----------------|----------------------------------------|-------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------------------|---------------------|
| Wild type      | 50 (6,800) [0.50]                      | 96                | 584                     | 503                     | 64                      | 15                      | 2                       | 0                       | 0.98                                | 1/102               |
| hhtz1Δ/hhtz1Δ  | 48 (6,841) [0.35]                      | 73                | 781                     | 320                     | 251                     | 102                     | 48                      | 60                      | 0.98                                | 1/102               |
| hho1Δ/hhtz1Δ   | 56 (6,795) [0.24]                      | 94                | 643                     | 533                     | 64                      | 41                      | 5                       | 0                       | 0.98                                | 1/127               |
| hhtz1Δ/hho1Δ   | 48 (2,601) [0.24]                      | 81                | 869                     | 415                     | 284                     | 127                     | 35                      | 8                       | 0.79                                | 1/127               |

Strain genotypes are described in the first column. Sporulation efficiency is the percentage of diploids that formed spores (either dyads, triads, or tetrads) when cells were placed under sporulation inducing conditions. The second column on the table shows percent spore viability; the total number of cells analyzed is listed in round brackets, the p-value in which each strain is compared to wild-type is listed in round brackets. P-values were calculated using a two-tailed Student’s t-test. The third column shows overall percent spore viability by strain as % (total number of spores that germinated/total number of spores analyzed). The fourth column lists the total number of tetrads analyzed for the spore viability experiment. Columns five through nine list the distribution of tetrads types based on number of spores that germinated per dissected tetrad. The last two columns list the frequency of chromosome III non-disjunction events by genotype; n.d., not determined.

Some htz1Δ meiocytes fail to establish a discrete chromosome axis

The SC is a conserved structure that mediates the alignment of homologous chromosomes during meiotic prophase, serving as the physical context for a large subset of meiotic recombination events (von Wettstein 1984; Zickler and Kleckner 1999; Page and Hawley 2003). The SC has a role in stabilizing paired homologs and regulating crossover formation (Page and Hawley 2003; Voelkel-Meiman et al. 2015, 2019). To examine the influence of H2A.Z and H1 on SC assembly, we performed cytological analysis of meiotic chromosomes on cells arrested at the pachytene stage of prophase I. Chromosomes were surface spread at 24 and 30 hr after their introduction into sporulation media and then immunolabeled using antibodies against the SC transverse filament protein, Zip1, and antibodies that target the Gmc2 and/or Ecm11 proteins (Fig. 4a). Zip1 forms transverse filaments of the yeast SC (Sym et al. 1993; Sym and Roeder 1995; Symington et al. 2014) while Ecm11 and Gmc2 localize to the central element of the budding yeast SC (Humphries et al. 2013; Voelkel-Meiman et al. 2013). We assigned nuclei stained for Zip1 protein to one of 4 categories: linear, diffuse, dotty linear, and dotty (illustrated in Fig. 4a and tabulated in Fig. 4b). All strains are homozygous ndi80A::LEU2, allowing for the enrichment of cells at the pachytene stage of meiosis. At 24 hr post-meiotic induction, the majority of meiotic nuclei of the wild-type strain exhibit extensive linear Zip1 linear structures that are coincident with linear Ecm11-Gmc2 and colocalized with the axes of DAPI-labeled chromosomes, as previously reported (Voelkel-Meiman et al. 2013). A minority of wild-type cells show a dotty linear or dotty Zip1 distribution on pachytene chromosomes, where Zip1 structures also coincide with the central element proteins Ecm11-Gmc2. The Zip1 and Ecm11-Gmc2 staining pattern and distribution of the linear and nonlinear classes are not significantly altered in the strain lacking histone H1 (Fig. 4b and Supplementary Fig 1). However, while full-length SC structures were observed in some htz1Δ meiotic nuclei, the fraction with mature SC structures is significantly reduced in this strain (Fig. 4b), indicating a defect or delay in SC assembly. A fraction of cells lacking H2A.Z exhibits an unusual SC morphology that we termed “diffuse” (Fig. 4a). Nuclei that display the diffuse phenotype exhibit Zip1 and Ecm11-Gmc2 staining that is uniformly coincident with the DAPI-labeled DNA, but in a disorganized, diffuse pattern. Nuclei with a diffuse phenotype are rare or absent in the wild-type and hho1Δ strains (Fig. 4b). A similarly diffuse distribution of Ecm11-Gmc2 is found in this category of nuclei (Supplementary Fig. 2). In contrast to the SC proteins we examined, the non-SC protein tubulin exhibited discrete, specific at individual loci. If we consider the hho1Δ and hhtz1Δ hho1Δ tetrad with exactly 2 gene conversions (17 events), we find that the gene converted markers are not more likely to be adjacent to one another than is expected by chance, suggesting that the elevated rates of gene conversion in these strains are due to an increase in the number of interhomolog (noncrossover) recombination events, vs extended gene conversion tracts spanning multiple markers.
staining in these chromosome spreads (Supplementary Fig. 3). Cells lacking histone H1 exhibit Zip1 and Ecm11-Gmc2 staining patterns indistinguishable from wild-type cells (Fig. 4b and Supplementary Fig. 1), and we observe that loss of H1 does not suppress or exacerbate the diffuse phenotype caused by the loss of H2A.Z (Fig. 4b).

Formation of the SC depends on the prior establishment of a chromosome axis scaffold, formed in part by the Rec8, Red1, and Hop1 proteins (Hollingsworth et al. 1990; Smith and Roeder 1997; Klein et al. 1999). To investigate the influence of H2A.Z on meiotic chromosome axis formation, we analyzed Red1 and Rec8 localization in cells progressing through meiosis (Fig. 5, a and b and Supplementary Fig. 4). We observe that Red1 partially coincides with Zip1 and Gmc2 in wild-type cells, but is not as continuous, as previously observed (Klein et al. 1999; West et al. 2019; see top row of Fig. 5a). Cells lacking histone H1 exhibit Red1 and Rec8 staining patterns indistinguishable from wild-type cells (Supplementary Figs. 5 and 6). In the majority of cells lacking H2A.Z, Red1 staining appears indistinguishable from wild-type cells (Fig. 5a). However, in cells exhibiting a diffuse Gmc2 distribution pattern, Red1 exhibits the same diffuse distribution pattern. Rec8 is a meiosis-specific subunit of the cohesion complex important for axis formation (reviewed in Govin and Berger 2009; Neiman 2011; Hunter 2015; Jaiswal et al. 2017; Hong et al. 2019). We used a strain heterozygous for a REC8-MYC allele to observe Rec8 localization. In wild-type meiotic prophase cells, Rec8-Myc is predominantly dotty linear (Fig. 5b), as previously observed (Klein et al. 1999; Challa et al. 2019). In the absence of H2A.Z, a fraction of cells exhibit a diffuse Rec8-Myc pattern, in which the
## Table 3. Genetic maps distances.

| Genotype        | Interval (chromosome) | PD | TT | NPD | Total | cM (± SE) | % WT | % WT by chrm | NPDobs/NPDexp | SE |
|-----------------|-----------------------|----|----|-----|-------|-----------|------|--------------|---------------|----|
| Wild type       | HIS4-CEN3 (III)       | 230| 251| 4   | 485   | 28.4 (1.6)| 100  | 103.5 (III)  | 100           | 0.14 (0.07) |
|                 | CEN3-MAT (III)        | 320| 165| 4   | 489   | 19.3 (1.6)| 100  | 0.26 (0.02)  |               | 0.43 (0.22) |
|                 | MAT-RAD18 (III)       | 176| 305| 6   | 487   | 35.0 (1.7)| 100  | 0.11 (0.05)  |               | 0.36 (0.18) |
|                 | AD18-HMR (III)        | 306| 179| 4   | 489   | 20.8 (1.6)| 100  | 84.6 (VIII)  | 100           | 0.33 (0.09) |
|                 | SPO11-SPO13 (VIII)    | 166| 301| 17  | 484   | 41.6 (2.5)| 100  | 0.84 (0.60)  |               | 0.04 (0.06) |
|                 | SPO13-THR1 (VIII)     | 386| 89 | 2   | 477   | 10.6 (1.2)| 100  | 0.12 (0.06)  |               |               |
| htz1Δ/htz1Δ     | HIS4-CEN3 (III)       | 127| 168| 7   | 502   | 34.8 (2.7)| 123  | 118.6 (III)  | 115           | 0.32 (0.13) |
|                 | CEN3-MAT (III)        | 181| 125| 2   | 308   | 22.2 (1.9)| 115  | 0.22 (0.16)  |               |               |
|                 | MAT-RAD18 (III)       | 87 | 214| 6   | 307   | 40.7 (2.5)| 116  | 0.22 (0.06)  |               |               |
|                 | AD18-HMR (III)        | 180| 129| 0   | 309   | 20.9 (1.4)| 101  | n.d.         |               |               |
|                 | SPO11-SPO13 (VIII)    | 114| 176| 14  | 304   | 42.8 (3.5)| 103  | 82.24 (VIII) | 97            | 0.27 (0.17) |
|                 | SPO15-THR1 (VIII)     | 257| 46 | 0   | 303   | 7.6 (1.0)| 72   | n.d.         |               |               |
| hho1Δ/hho1Δ     | HIS4-CEN3 (III)       | 215| 290| 5   | 510   | 31.4 (1.6)| 111  | 111.33 (III) | 108           | 0.13 (0.06) |
|                 | CEN3-MAT (III)        | 349| 172| 0   | 521   | 16.5 (1.0)| 85   | n.d.         |               |               |
|                 | MAT-RAD18 (III)       | 186| 312| 15  | 513   | 39.2 (2.3)| 112  | 0.30 (0.09)  |               |               |
|                 | AD18-HMR (III)        | 285| 226| 4   | 515   | 24.3 (1.5)| 117  | 0.21 (0.11)  |               |               |
|                 | SPO11-SPO13 (VIII)    | 171| 326| 19  | 516   | 42.6 (2.4)| 102  | 82.59 (VIII) | 98            | 0.32 (0.08) |
|                 | SPO13-THR1 (VIII)     | 391| 107| 1   | 499   | 11.3 (1.1)| 107  | 0.30 (0.30)  |               |               |
|                 | THR1-LYS2 (VIII)      | 119| 180| 2   | 301   | 31.9 (1.9)| 98   | 0.07 (0.05)  |               |               |
| htz1Δ/hho1Δ     | HIS4-CEN3 (III)       | 166| 192| 7   | 365   | 32.1 (2.4)| 113  | 118.02 (III) | 114           | 0.32 (0.13) |
|                 | CEN3-MAT (III)        | 211| 154| 2   | 367   | 22.6 (1.7)| 117  | 0.17 (0.12)  |               |               |
|                 | MAT-RAD18 (III)       | 124| 234| 6   | 364   | 37.1 (2.1)| 106  | 0.13 (0.06)  |               |               |
|                 | AD18-HMR (III)        | 195| 158| 5   | 358   | 26.3 (2.2)| 126  | 0.38 (0.18)  |               |               |
|                 | SPO11-SPO13 (VIII)    | 125| 220| 18  | 363   | 45.2 (3.5)| 109  | 82.02 (VIII) | 97            | 0.51 (0.14) |
|                 | SPO13-THR1 (VIII)     | 286| 69 | 0   | 355   | 9.7 (1.1)| 92   | n.d.         |               |               |
|                 | THR1-LYS2 (VIII)      | 167| 186| 1   | 354   | 27.1 (1.5)| 84   | 0.05 (0.05)  |               |               |

Four spore viable tetrads with no more than two gene conversion events each were used for the measurement of map distances and crossover interference as described in (Voelkel-Meiman et al., 2015). The specific intervals investigated for recombination efficiency are listed; the number of parental ditypes (PD), tetratypes (TT) and nonparental ditypes (NPD), map distance (in centimorgans; cM), the associated percentage of wild-type for individual intervals and for the entire chromosome (chrom). Interference is represented on the table as the ratio of observed (obs) to the expected (exp) NPD tetrads. (n.d.) means crossover interference could not be determined due to lack of nonparental ditype (NPD) tetrads.

**Discussion**

Chromatin structure influences various aspects of the meiotic program. Here, we have extended earlier studies that established unique roles of the linker histone H1 and variant histone H2A.Z in progression through meiosis. Prior work identified a role for histone H1 in inhibiting homologous recombination in mitotic cells, both in the context of double-strand break repair (Downs et al. 2003) and in the suppression of recombination at the rDNA repeats (Li et al. 2008). However, initial experiments examining meiotic recombination over 4 intervals on chromosome XV failed to observe changes in meiotic recombination frequency in diploids lacking histone H1 (Brush 2015). We measured recombination over 7 intervals on chromosomes III and VIII in cells lacking H1 and did not observe significantly altered recombination frequencies, suggesting that H1 does not regulate homologous recombination in meiotic cells (Fig. 2b). Consistent with prior experiments examining a single interval on chromosome VIII (Gonzalez-Arranz et al., 2018), we also observe no significantly altered recombination frequencies over 7 distinct intervals in strains lacking histone H2A.Z. However, htz1Δ cells exhibit an elevated cumulative increase in recombination across chromosome III. We also observed a chromosome III-specific increase in gene conversion in strains lacking H2A.Z. These data suggest that H2A.Z impacts chromosome III structure in a manner that regulates either meiotic recombination initiation (DNA double-strand break formation) or the likelihood of a meiotic double-strand break engaging the homologous chromosome for repair. Interestingly, Lee et al. (2021) have recently reported chromosome III-specific decreases in recombination in yeast strains lacking............................................................................................................
Table 4. Frequency of gene conversion in strains lacking H2A.Z and H1.

| Genotype          | # 4—9 spore viable tetrads | % tetrads with ≥1 gene conversion (GC) | % tetrads with ≥1 GC | P-Value | Total GCs | GCs per tetrad | P-Value | GCs per tetrad versus wild type | % total GCs chrom III | % total GCs chrom VIII | # tetrads without a GC | P-Value |
|-------------------|-----------------------------|----------------------------------------|---------------------|---------|-----------|----------------|---------|--------------------------------|----------------------|------------------------|------------------------|---------|
| Wild type         | 497                         | 42                                     | 8                   | N.A.    | 63        | 0.13           | N.A.    | 1                              | 44                   | 56                     | 455                    | N.A.    |
| hho1Δ/htz1Δ       | 314                         | 34                                     | 13                  | 0.26    | 42        | 0.13           | 0.77    | 1                              | 36                   | 64                     | 280                    | 0.2975  |
| hho1Δ/htz1Δ       | 530                         | 64                                     | 12                  | 0.066   | 91        | 0.17           | 0.044   | 1.3                            | 45                   | 55                     | 466                    | 0.0645  |
| hho1Δ/htz1Δ       | 396                         | 68                                     | 17                  | 0.0001  | 150       | 0.38           | <0.0001 | 2.9                            | 75                   | 25                     | 328                    | <0.0001 |

Only four spore viable tetrads were used for the analysis of gene conversions (GC). Percentage of tetrads carrying at least one GC was slightly elevated in the absence of H1 and H2A.Z. We used the two proportions Z-test to analyze the significance of difference in GC frequency by comparing the knockout strains to the wild-type. Total number of GC for each strain was used to calculate GC per tetrad. The hho1Δ and htz1Δ hho1Δ strains have significantly more GC per tetrad compared to the wild-type. The last column shows Fisher’s exact test comparing gene conversion versus non-gene conversion tetrads per strain. Each strain was compared to the wild-type, N.A., not applicable.

Fig. 4. A subset of cells lacking H2A.Z have SC defects. a) Meiotic cell nuclei were surface-spread on glass slides, fixed and stained for the Zip1 and Ecm11-Gmc2 SC proteins (the antibody targeting Ecm11-Gmc2 was raised against a complex of the 2 proteins). Strains examined are homozygous for ndt80Δ (Xu et al. 1995) and thus fail to progress beyond a late prophase stage of meiosis when SC structures are normally full length. Representative images for wild-type and htz1Δ cells are shown. Images for the hho1Δ strain are shown in Supplementary Fig. 1. Nuclei were categorized based on Zip1 or Ecm11-Gmc2 staining: linear, long continuous linear structures; dotty linear, a mixture of foci and short linear structures; dotty nuclei, only foci of Zip1, diffuse, a disorganized distribution that is coincident with DAPI. All strains used for cytological analysis are homozygous ndt80Δ::LEU2, causing arrest at pachytene of prophase I. Scale bar is 1 μm. b) Distribution of SC structures in all experimental diploids based on Zip1 staining. At least 100 nuclei were analyzed for each strain, from at least 3 independent experiments. Time (x-axis) is time post meiotic induction. The number of nuclei assessed for each strain is indicated. An analysis of Ecm11-Gmc2 staining is shown in Supplementary Fig. 2.
**Fig. 5.** H2A.Z promotes meiotic chromosome axis assembly or maintenance. 

a) A subset of cells lacking H2A.Z has defective chromosome axes. Meiotic chromosomes were surface-spread at 24 hr after introduction into sporulation media, and labeled with antibodies targeting Red1 and Gmc2. Representative images show the different categories used to assess the state of the SC based on Gmc2 staining, as defined as in the legend of Fig. 4a. 

b) Representative images for chromosomes stained for Rec8-Myc and Ecm11-Gmc2. Scale bar is 1 µm.
Gmc2 or Ecml. Distinct features of chromosome III include its relatively small size, its participation in cell type-specific recombination to mediate mating type switching, and the presence of the HML and HMR heterochromatic regions. One or more of these properties may influence recombination.

In agreement with a prior report (Gonzalez-Arranz et al. 2018), we observed a significant decrease in spore viability in strains lacking H2A.Z. Decreased spore viability is frequently a consequence of defects in chromosome segregation. Our failure to observe an increase in nonmating spores in 2-spore viable tetrads suggests that the decrease in viability is not due to nondisjunction in meiosis I. Instead, the high number of 3-spore viable tetrads (Fig. 1c and Table 2) is consistent with premature sister chromatid separation in MI or chromosome nondisjunction during MI (Rockmll et al. 2006; Chu and Burgess 2016). H2A.Z is required to promote chromosome stability in budding yeast during vegetative growth (Krogan et al. 2004; Keogh et al. 2006, Sharma et al. 2013). Vegetatively growing cells lacking histone H2A.Z have defects in chromosome cohesion (Sharma et al. 2013) and condensation (Rogers and Holmes, unpublished). Compromised condensin protein function causes meiotic defects, including decreased axial compaction (Yu and Koshland 2003; Brito et al. 2010; Li et al. 2014). It was recently shown that H2A.Z localizes to the spindle pole body and promotes normal chromosome movement during budding yeast meiosis (Gonzalez-Arranz et al. 2020). Thus, H2A.Z could contribute to chromosome stability in meiosis by multiple mechanisms. Given the role H2A.Z has in maintaining chromosome stability in mitotic cells, some fraction of htz1A cells are likely aneuploid when entering meiosis (although these cells would not be predicted to cause an increase in 3 spore viable tetrads).

While strains missing only histone H1 have spore viability comparable to wild-type cells (Bryant et al. 2012; Brush 2015; this study), we find that eliminating HHO1 can partially suppress the spore viability defect in htz1A cells (Fig. 1b). We have observed that the condensation defect observed in mitotic cells lacking H2A.Z can be partially suppressed by also eliminating histone H1 (Rogers and Holmes, unpublished). In addition, spores from budding yeast that lack histone H1 are reported to have slightly larger nuclear area than spores from wild-type cells, suggesting that their chromatin is relatively decondensed (Bryant et al. 2012). Schizosaccharomyces pombe strains expressing htz1A mutant phenocopies the htz1A diffuse phenotype addition to whether this defect could be rescued by the overexpression of Rec8 meiotic cohesion.

**Data availability**

All yeast strains described in this study are available from the authors upon request. The authors affirm that all data necessary for confirming the conclusions of the article are present within the article, figures, and tables.

**Supplemental material** is available at G3 online.

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**Conflicts of interest**

None declared.

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