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How do small chromosomes know they are small? Maximizing meiotic break formation on the shortest yeast chromosomes

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Abstract

The programmed formation of DNA double-strand breaks (DSBs) in meiotic prophase I initiates the homologous recombination process that yields crossovers between homologous chromosomes, a prerequisite to accurately segregating chromosomes during meiosis I (MI). In the budding yeast *Saccharomyces cerevisiae*, proteins required for meiotic DSB formation (DSB proteins) accumulate to higher levels specifically on short chromosomes to ensure that these chromosomes make DSBs. We previously demonstrated that as-yet undefined *cis*-acting elements preferentially recruit DSB proteins and promote higher levels of DSBs and recombination and that these intrinsic features are subject to selection pressure to maintain the hyperrecombinogenic properties of short chromosomes. Thus, this targeted boosting of DSB protein binding may be an evolutionarily recurrent strategy to mitigate the risk of meiotic mis-segregation caused by karyotypic constraints. However, the underlining mechanisms are still elusive. Here, we discuss possible scenarios in which components of the meiotic chromosome axis (Red1 and Hop1) bind to intrinsic features independent of the meiosis-specific cohesin subunit Rec8 and DNA replication, promoting preferential binding of DSB proteins to short chromosomes. We also propose a model where chromosome position in the nucleus, influenced by centromeres, promotes the short-chromosome boost of DSB proteins.

Introduction

Meiosis starts with one round of DNA replication followed by two rounds of chromosome segregation to reduce the genome complement in gametes, for example producing haploid reproductive cells from diploid progenitor cells. Meiotic recombination is initiated by

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programmed formation of DSBs by Spo11 along with a number of accessory proteins ("DSB proteins") that include Rec114 and Mer2 (Lam and Keeney 2015), which function with Mei4 to form chromosome associated "RMM" assemblies (Arora et al. 2004; Li et al. 2006; Maleki et al. 2007; Claeys Bouuaert et al. 2020). Recombination yields crossovers that help provide physical connections between homologous chromosomes, prerequisites for proper chromosome segregation in MI (Hunter 2015). Thus, accurate chromosome segregation in MI requires faithful allocation of at least one DSB per pair of homologs in meiotic prophase I.

Chromosomes of different sizes behave differently with respect to the density of DSBs and thus of recombination events (Kaback et al. 1992; Chen et al. 2008; Mancera et al. 2008; Pan et al. 2011). In exploring these differences, we found that temporally distinct pathways regulate when DSB proteins associate and then dissociate from each chromosome, thereby controlling the duration of a DSB competent state (Murakami and Keeney 2014; Murakami et al. 2020). This control of DSB competence helps ensure that all chromosomes have the opportunity to break and recombine. We also found that one of these pathways involves "intrinsic features" that are embedded in short chromosomes and that promote a rapid and high-level association of DSB proteins (Fig. 1A**, left**). We refer to this phenomenon as the "short-chromosome boost." This boost is deduced to function in *cis* because a chromosomal region from a short chromosome still specifically boosts DSB protein binding when artificially fused to a long chromosome (Murakami et al. 2020). The boost proactively controls DSB potential to ensure the segregation of chromosomes that are difficult to recombine, and the strategy is potentially widespread in evolution (Acquaviva et al. 2020; Murakami et al. 2020). However, it remains unclear what the intrinsic features are and how they promote the boost. We discuss potential mechanisms here.

Which protein boosts first?

Hop1, Red1 and cohesin are prominent proteins assembling chromosome axes in meiotic prophase, and they promote multiple aspects of meiotic recombination including DSB formation (Hollingsworth et al. 1990; Mao-Draayer et al. 1996; Smith and Roeder 1997; Klein et al. 1999; Woltering et al. 2000; Blat et al. 2002; Niu et al. 2005; Carballo et al. 2008; Panizza et al. 2011). Red1 is a relative of mammalian axis protein SYCP3 (West et al. 2019); Hop1 contains a HORMA domain that mediates regulated protein-protein interactions with Red1 (West et al. 2018); and Rec8 is a meiosis-specific kleisin component of cohesin (Klein et al. 1999). These axis proteins are required for efficient association of DSB proteins to chromosomes (Panizza et al. 2011), but the individual mutants confer distinct boost phenotypes. The *red1* and *hop1* single and double mutants lose the boost on short chromosomes, whereas the *rec8* mutant maintains the boost (Murakami et al. 2020). Moreover, chromatin immunoprecipitation (ChIP) experiments showed that Red1 and Hop1 preferentially bind to short chromosomes, while Rec8 does not (Sun et al. 2015; Subramanian et al. 2019). These findings suggest that meiosis-specific axis proteins Hop1 and Red1 may be the key factors promoting the DSB protein boost on short chromosomes.

Hop1 binding is highly dependent on Red1 (Sun et al. 2015; Markowitz et al. 2017). In contrast, Red1 binds to chromosomes in the absence of Hop1 albeit with a modest decrease

in ChIP signal to ~70% of wild type (Vale-Silva et al. 2019). Interestingly, however, absence of Hop1 leads to the loss of the Red1 preferential binding on short chromosomes (Sun et al. 2015; Vale-Silva et al. 2019). Moreover, Red1 and Hop1 can bind chromatin even in the absence of Rec8, although decreased in the amount (~40% of wild type for Red1) and with altered distribution of binding throughout the genome (Panizza et al. 2011; Sun et al. 2015; Vale-Silva et al. 2019). Importantly, the preferential binding of Red1 and Hop1 to short chromosomes is independent of Rec8: *rec8* mutants maintain high levels of overrepresentation relative to long chromosomes (see also below) (Fig. 1B) (Panizza et al. 2011; Sun et al. 2015; Vale-Silva et al. 2019; Heldrich et al. 2020). One possible interpretation could be that Hop1 stabilizes Red1 independently of Rec8 by preferentially binding to intrinsic features on short chromosomes, leading to boosting of both Red1 and Hop1, as well as DSB proteins (Fig. 1A**, right**). A similar model has been previously proposed (Sun et al. 2015). If this is the case, preferential binding of Hop1 to short chromosomes is likely to be a key to elucidate the boosting mechanism.

Chromosomal binding of Hop1 is modulated by the AAA+ ATPase Pch2 (TRIP13 in mammals). Upon synapsis of chromosomes, recruitment of Pch2 leads to redistribution and/or dissociation of Hop1 from axes (Börner et al. 2008; Wojtasz et al. 2009; Chen et al. 2014; Rosenberg and Corbett 2015; Subramanian et al. 2016). Pch2 may also facilitate Hop1 association by increasing the cellular pool of a Hop1 conformation that is competent to bind to chromosomes (Raina and Vader 2020). We therefore speculated that Pch2 might be involved in promoting the preferential binding of Hop1 to short chromosomes. However, *pch2* mutants still show overrepresentation of Hop1 on short chromosomes (Fig. 1C), thus Pch2 does not appear to play a major role in establishing this boost.

When does the boost occur?

The preferential binding to short chromosomes of axis proteins Red1 and Hop1 and DSB proteins Rec114 and Mer2 appears early in meiotic prophase (already detectable at 2 h after meiosis induction) (Subramanian et al. 2019; Murakami et al. 2020). This is the time when premeiotic DNA synthesis is most prominent (Blitzblau et al. 2012), which might have pointed to involvement of replication in establishing the boost. However, we showed that this is unlikely to be the case. Rec114 association to chromatin is spatiotemporally coupled to replication fork passage, which requires components of the replication fork protection complex, Tof1 and Csm3 (Murakami and Keeney 2014). Absence of Tof1 disrupts coordination between Rec114 association and replication, but the *tof1* mutant still shows the Rec114 boost (Murakami et al. 2020). Furthermore, the Hop1/Red1 boost is independent of meiotic replication (Fig. 1D) (Blitzblau et al. 2012). Thus, it is likely that Hop1 and Red1 and/or some DSB proteins also start binding preferentially to short chromosomes early in meiotic prophase, possibly before replication. The Mer2 foci seen at the entry of meiotic prophase I (Henderson et al. 2006) may reflect these initial associations.

Where are the intrinsic features?

We hypothesize that initial binding of Hop1 and Red1 to preferred sites (the aforementioned intrinsic features) is followed by relocation tied to cohesins sliding along chromosomes.

Red1 appears to bind to chromatin at least in part through physical interactions with Rec8 (Sun et al. 2015). Red1 functions as the axial core (West et al. 2019) and recruits Hop1 via interaction between the HORMA domain in Hop1 and a closure motif in Red1 (West et al. 2018). Consistent with these interactions, Hop1, Red1 and DSB proteins show similar chromosomal distributions with strong enrichment at convergent intergenic regions (IGRs) (Panizza et al. 2011; Sun et al. 2015). These binding patterns are likely shaped by the distribution of cohesin, which is under the influence of being pushed by the transcription machinery towards transcription termination regions (Lengronne et al. 2004) and, possibly, by the active translocation of cohesin complexes that is proposed to drive loop extrusion (Muller et al. 2018; Schalbetter et al. 2019). Hop1, Red1 and DSB proteins may thus travel with cohesins to convergent IGRs through the above interaction (Sun et al. 2015) as well as interaction between Hop1 and Mer2 (Kariyazono et al. 2019; Rousova et al. 2020), and interactions among DSB proteins (Arora et al. 2004; Henderson et al. 2006; Li et al. 2006; Maleki et al. 2007) (Fig. 1E). An alternative to this pushing model is that binding of Hop1, Red1 and DSB proteins is inhibited by transcription and can only nucleate stably where transcription is not occurring, or that the various components mutually reinforce their binding to each other so that in wild type one sees predominantly the locations where cohesin has accumulated because of pushing.

However, despite the importance of cohesin, as noted above, multiple lines of evidence suggest that Hop1 and Red1 can associate with chromatin independently of cohesin. First, Hop1, Red1 and the DSB proteins Rec114, Mer2, and Mei4 can all bind DNA independently *in vitro* (Kironmai et al. 1998; Kshirsagar et al. 2017; Rousova et al. 2020; Claeys Bouuaert et al. 2020). Second, Red1 and DSB proteins can bind to chromatin and promote DSB formation in the absence of Rec8, albeit with significantly altered distributions, thus defining both Rec8-dependent and -independent chromosomal domains (Kugou et al. 2009; Panizza et al. 2011; Sun et al. 2015; Vale-Silva et al. 2019; Heldrich et al. 2020). Interestingly, the three shortest chromosomes contain Rec8-independent domains for almost their entire lengths and maintain the Red1 and Hop1 overrepresentation. Third, a triple mutant lacking all three of these axis components (*rec8 hop1 red1*) retains high levels of Rec114 chromatin binding even though it is unable to efficiently form DSBs (Murakami et al. 2020).

Cohesins traveling along chromosomes may pick up their passengers (Hop1/Red1 and DSB proteins) waiting at their initial binding sites and bring all together to final destinations (enriched at convergent IGRs). If this is the case, the distributions of Hop1, Red1 and DSB proteins in wild type may not coincide precisely with locations of the intrinsic *cis*-acting features initially responsible for their high-level binding. It may be necessary to use mutants in which Hop1 and Red1 stay at their initial binding sites (e.g., *rec8*) to identify locations of these intrinsic features (Fig. 1E).

What are the intrinsic features?

Since the boosting feature of segments from a short chromosome is stably inherited after the segments have been translocated onto larger chromosomes (Fig. 1A**, left**), the intrinsic features are likely to be defined genetically (i.e., by DNA sequence) rather than epigenetically. However, it is unclear whether Hop1 (and/or other proteins) recognizes the

DNA sequence(s) directly or if recognition is indirect via chromatin features promoted by the sequence.

One possible scenario could be that Hop1 and/or Red1 prefer to bind to GC-rich sequences, which are enriched on short chromosomes (Muniyappa et al. 2000; Blat et al. 2002; Kshirsagar et al. 2017) (Fig. 1F). However, the degree of GC overrepresentation is not as extreme as the overrepresentation of DSB proteins and DSBs on the three shortest chromosomes (compare Figs. 1B-D and 1F). Moreover, it is not yet clear whether higher GC content is a cause or consequence of higher recombination rates.

We have searched within Rec114 ChIP-seq peaks for sequence motifs that might be responsible for preferential recruitment of Red1, Hop1, and/or DSB proteins. We used wild-type ChIP-seq peaks but also peaks called specifically in the *rec8* mutant. However, we have not yet succeeded in discovering significant candidate motifs. Alternatively, such motifs might not exist within the above search space, since the gene density and gene length correlate with Red1 ChIP signal in *rec8* (Sun et al. 2015; Heldrich et al. 2020). Thus, the identity of the intrinsic feature(s) remains to be determined.

Do other properties of short chromosomes promote preferential Hop1 recruitment?

In addition to the inferred intrinsic features recruiting Hop1, we speculate that centromeres may also be involved. The Boeke laboratory and collaborating groups created fusion chromosomes consisting of different size chromosomes (Luo et al. 2018). To prevent fused chromosomes from having multiple centromeres, one centromere was left active, and others were deleted. Interestingly, the segments that originated from short chromosomes showed a boost in Red1 binding only when the original centromere of the short chromosome was maintained (Luo et al. 2018). Although our artificial translocation chromosomes showed the boost even without their original centromere, the centromere from the long chromosome is right next to the attached region derived from the short chromosome (Murakami et al. 2020). Thus, these findings raise the possibility that the boost requires the intrinsic features embedded in short chromosomes plus the presence of a functional centromere nearby.

Here we propose a model that integrates current insights (Fig. 1G). During mitotic interphase, centromeres are clustered together near the nuclear envelope through tethering to the spindle pole body (SPB) via microtubules, referred to as the Rabl orientation (Burgess and Kleckner 1999; Jin et al. 2000; Lazar - Stefanita et al. 2017). Upon entry into meiotic prophase I, chromosomes exhibit a similar configuration (Jin et al. 1998; Muller et al. 2018; Schalbetter et al. 2019). We propose that the local concentration of Hop1 is high within a zone in the nucleus where centromeres are clustered, possibly due to nuclear transport of Hop1 through nuclear pore complexes enriched in the vicinity of the unduplicated SPB (Rüthnick et al. 2017). This scenario would create a “boost center” where chromosomes compete for a limited amount of Hop1 early in meiosis when Hop1 is first being synthesized. Because of their intrinsic features attracting Hop1, short chromosomes tend to win this competition, which leads to further preferential stabilization on short chromosomes of Red1 and Mer2, and later Rec114 and Mei4, reinforcing the boost. An alternative could

be that, because various proteins, including Hop1, preferentially bind centromeres in early meiotic prophase I (Kugou et al. 2009; Panizza et al. 2011; Subramanian et al. 2019; Murakami et al. 2020), centromeres might function as a reservoir that promotes local enrichment of these proteins. However, the finding that the *rec8* mutant eliminates the enrichment of Rec114 at centromeres but maintains the short chromosome boost (Murakami et al. 2020) argues against this scenario. Nonetheless, these scenarios are experimentally testable, so more detailed insight into the underlying molecular mechanisms should be obtainable.

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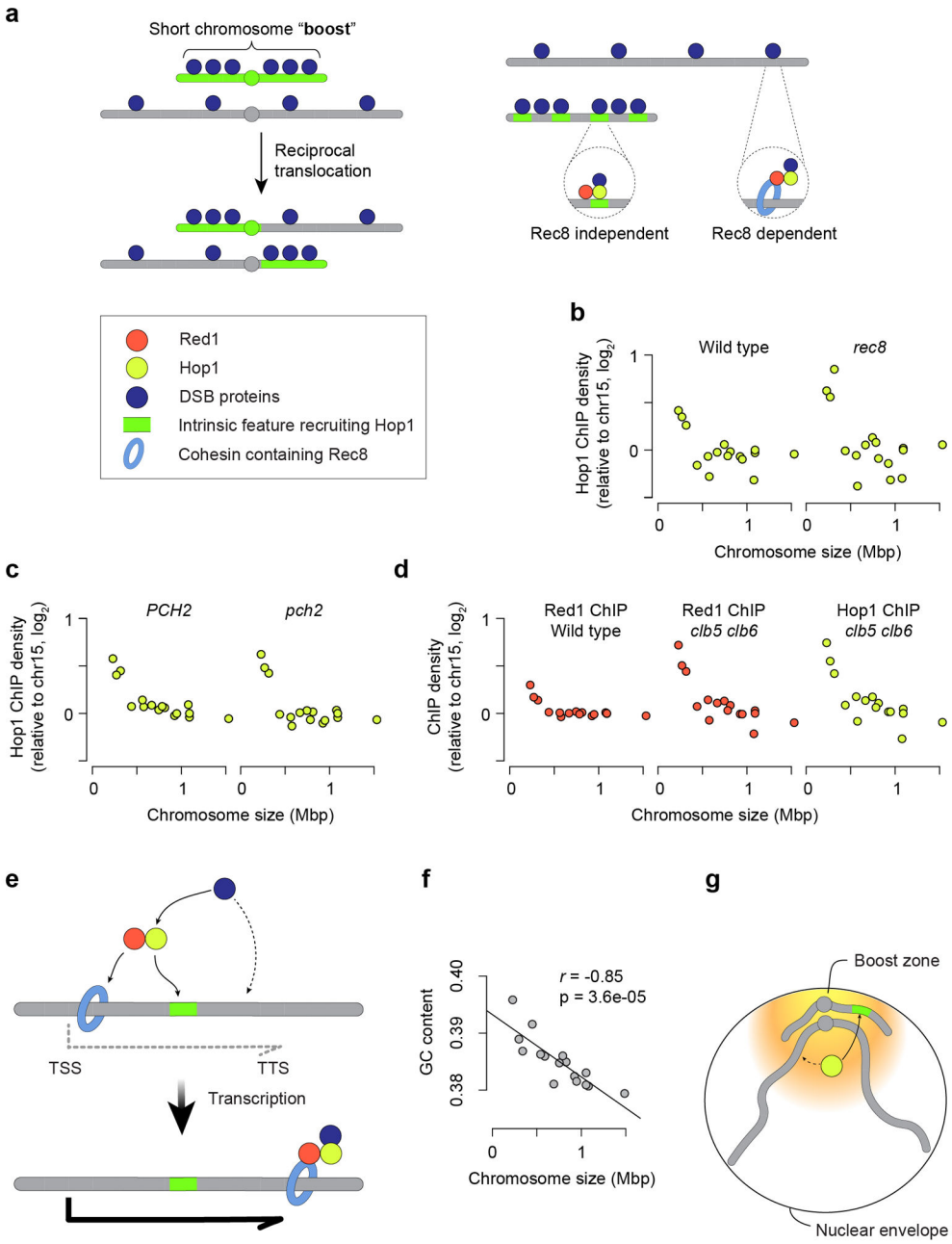

Fig. 1. Mechanisms by which intrinsic features promote the short-chromosome boost.

A Left: intrinsic features on short chromosome promote preferential DSB protein binding in *cis* (short chromosome boost). Right: two ways to recruit Red1 and Hop1. In addition to cohesin-dependent recruitment of Red1 and Hop1 (no chromosome-size dependent bias), intrinsic features preferentially (but not exclusively) recruit Hop1 to short chromosomes, stabilizing Hop1 and Red1 interactions and leading in turn to preferential DSB protein recruitment.

B Preferential binding of Hop1 on short chromosomes does not require Rec8. We used published Hop1 ChIP-chip data collected at 4 h in meiosis in wild type and *rec8* mutant (Panizza et al. 2011). ChIP signals were averaged on each chromosome and normalized to a

long chromosome (chr15) and plotted as a function of chromosome size. Similar Rec8-independent overrepresentation of Red1 was previously shown (Sun et al. 2015).
C Hop1 overrepresentation on short chromosomes does not require Pch2, a AAA+ ATPase proposed to promote Hop1 loading onto chromatin (Raina and Vader 2020). Published Hop1 ChIP-seq data at 3 h in meiosis (Subramanian et al. 2019) were processed as described in B. Note that both strains have the *ndt80* mutation, which arrests cells in prophase I.
D Hop1 and Red1 boost on short chromosomes is independent of meiotic DNA replication. Published Red1 and Hop1 ChIP-chip data at 4 h in meiosis in wild type and *clb5 clb6* mutants (deficient in the initiation of meiotic replication) (Blitzblau et al. 2012) were processed as described in B. Hop1 overrepresentation on short chromosomes presented in B and C was also previously shown (Panizza et al. 2011; Subramanian et al. 2019).
E Complexes of Hop1 and Red1 associate with chromatin in cohesin (Rec8) dependent and independent manners. Cohesin-independent binding is perhaps promoted by intrinsic features that recruit Hop1. DSB proteins also bind to chromatin in two ways (both dependent and independent of Hop1 and Red1). Transcriptional machinery pushes cohesin leading to the relocalization of all proteins towards transcription termination sites.
F Per-chromosome GC content was measured using a genome assembly of the *S. cerevisiae* SK1 strain (Yue et al. 2017). Pearson's correlation coefficient and p-value are shown.
G A model to explain the centromere requirement for establishing the short chromosome boost. We propose that free Hop1 is concentrated within a zone where centromeres are clustered at the entry stage of meiotic prophase I (illustrated as "boost zone"). Short chromosomes outcompete long chromosomes due to their comparative advantage in recruiting Hop1 through intrinsic boosting features located in the centromere vicinity.