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Telomeres in meiotic recombination: The Yeast Side Story

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Abstract. The aim of this review is threefold. First, we want to report on recent observations on the role of telomeres in the alignment of homolog and non-homologues in the yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* and the relationship of early telomere clustering to later recombination events. Second, we compare the similarities and differences between synaptic and asynaptic yeasts. Third, we report on the increasing evidence of the effect of meiosis on telomeric sequences that suggest an induction of a specific form of recombination processes termed telomere rapid deletion.

Keywords. Meiosis, telomere, recombination, bouquet structures, telomere clustering, meiotic prophase, synapsis, commitment.

Yeasts, telomeres and recombination

Meiotic recombination occurs both between homologous chromosomes and between the imperfect repeats present at the telomeres. Recombination is initiated at the start of meiotic prophase I in the pre-leptotene stages with the formation of double-stranded breaks (DSBs) and is completed towards the end of pachytene with formation of mature crossover products. Numerous meiotic-specific genes bias recombination towards the non-sister chromatid over sister chromatid exchange. The physical exchange products, or chiasmata, that are formed as a consequence of recombination, persist until late anaphase. Recombination is temporally coincident and functionally linked with other meiotic landmark events, including telomere clustering and dispersion, and homolog alignment and pairing.

The functional significance of telomeres in the production of meiotic recombinants, including telomere/telomere recombination, has attracted growing interest. Telomeres assemble into a centrosome/spindle pole body (SPB)-associated structure in the leptotene-zygotene transition of prophase I that are disassembled in late pachytene. Since telomeres are associated in one cluster and the rest of the chromosomes loop into the nucleus, the resulting cytological structure has been termed the bouquet structure. The bouquet is highly conserved across organisms and is temporally fixed in the meiotic cascade. It temporally coincides with the transition of the DSBs into double Holliday Junctions (dHJs). Also, bouquet formation and dissolution are actively regulated. These data point to the functional significance of the bouquet structure in meiosis. Moreover, in the fission yeast *Schizosaccharomyces pombe*, which lacks synaptic machinery [i.e, the synaptonemal complex (SC)], telomeres have a unique role of leading a vigorous movement of the chromosome bundle throughout the nucleus via attachment to cytoplasmic microtubules, presumably aligning homologs. In this review we will focus on the significance of telomeres in the meiotic process, especially its roles in meiotic recombination, in two model systems: *S. cerevisiae* and *S. pombe.*

Though both are unicellular yeasts, *S. pombe* and *S. cerevisiae* have widely divergent meiotic machineries and processes. *S. cerevisiae* undergoes synapsis, exhibits crossover interference (COI) and has limited nuclear oscillation in prophase. *S. pombe*, on the other hand, is asynaptic, does not have COI, and has a rather dramatic and extended phase of nuclear movement termed the horsetail [1]. Also, proteinaceous structures called linear elements (LEs) substitute for axial elements (AEs) in this organism [2] The proteins that facilitate these processes are also widely divergent between these organisms, as are their number of chromosomes (32 chromosomes in a *S. cerevisiae* diploid with 64 telomeres composed of around 300 bp of a C1–3A/TG1–3 irregular repeat sequence).

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In contrast, *S. pombe* diploids have 6 chromosomes and therefore 12 telomeres that are approximately 200–300 bp long, and have a G_{2-8}TTAC (A) repeat sequence. Studies of meiosis in these two organisms are likely to offer a broad perspective of the meiotic themes found in nature.

S. cerevisiae

Cytological studies

At the cytological level, efficient meiotic recombination in *S. cerevisiae* appears to require several distinct steps: (i) homologous alignment and stable juxtaposition in part due to telomere clustering; (ii) specific DSB regions that initiate recombination; (iii) A structural support (the SC) during the formation of recombination intermediates; (iv) mechanisms to prevent promiscuous ectopic recombination; and (v) chiasmata that ensure proper segregation of chromosomes during reductional division. It is important to note that these are not all isolated independent events but part of an interdependent network that drives efficient genetic recombination (Fig. 1).

Chromosomes in *S. cerevisiae* diploids in mitotic interphase are arranged in the Rabl orientation, with centromeres clustered in one spot close to the SPB and the telomeres on the opposing side. Telomeres are grouped as 2–8 spatially constrained small clusters tethered to the nuclear envelope [3]. Homologous chromosomes are paired in vegetative G1/G0 diploid cells [4]. A round of premeiotic DNA replication precedes the abrupt loss of centromere clustering and centromere/SPB association, marking entry into meiosis (Fig. 1). Dispersion of telomeres on the nuclear envelope occurs towards the end of premeiotic S-phase [5]. Interestingly, vegetative telomere and centromere dispersion are independent events [6].

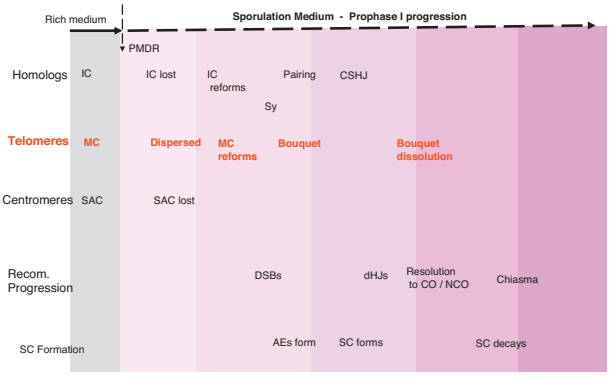

Figure 1. Timing of the bouquet in relation to other meiotic events of *S. cerevisiae.* The bouquet coincides with major meiotic landmarks. The increase in the background hue represents progression through meiosis. IC, interstitial contacts; MC, miniclusters; SAC, SPB-associated clustering; AE, axial elements; SC, synaptonemal complex; CO/NCO, crossovers and non-crossovers; Sy, synizetic knot; PMDR, premeiotic DNA replication.

The vegetative homolog pairing is dissolved at the start of meiotic prophase and then apparently reestablished after premeiotic DNA replication [4]. Homolog recognition is independent of both recombination and synapsis [7]. Pairing has been variably used in the literature to reference both the initial colocalization and alignment and subsequent close stable juxtaposition of homologs. Throughout this manuscript we will define pairing as the alignment of chromosomes adjacent to each other following a homology search. We will refer to the more stable and intimate association of homologs that are formed immediately prior to strand invasion as close stable homolog juxtaposition (CSHJ) [8]. In budding yeast, homologs are first associated in a segmented fashion, before end-to-end alignment [9, 10]. While CSHJs are stabilized by SCs, SC formation is not an absolute requirement for meiotic recombination [7].

Prior to the assembly of the bouquet, the chromosomes cluster into a dense cytological structure called the synizetic knot [11]. As meiosis progresses, telomeres dispersed on the envelope assemble into small clusters before clustering into a bouquet [3]. Nuclei become elliptical, and subtle translational movements of nuclei are observed [12]. This differs from the extended dramatic nuclear movements seen in *S. pombe*. Meiotic recombination is initiated soon after premeiotic DNA replication during DSB formation. DSBs form at the leptotene, the same meiotic stage where the bouquet is initiated, homolog pairing is detected and axial elements form. The DSBs are resected to form 3′ overhangs that invade into the paired homologs through single-end invasions and form dHJ intermediates that are resolved as CO and NCO. CO result in chiasmata and occur when the dHJ is resolved without exchange of flanking regions. NCO occurs when the dHJ is resolved without exchange of chromosomal arms. Most of the estimated 175–260 recombination events [13] that occur in meiosis are non-randomly resolved as NCOs. Only a few (~90 in the entire genome) are resolved as COs [14]. The bias is probably directed by a group of interesting proteins (the ZMM class of proteins) that stabilize early strand invasion intermediates.

The timing of bouquet formation precedes homolog pairing. Cytological observations [15] coupled with elegant genetic studies in synchronous meioses [9, 10] argue for an essential catalytic role for the bouquet in homolog pairing. However, fluorescence in situ hybridization (FISH) observations imply multiple interstitial contacts that are present in the vegetative state but lost during premeiotic DNA replication are reestablished prior to the bouquet, raising the possibility of a non-telomeric redundant pathway [4]. Alternatively, the bouquet may be important in the progression of the interstitial contacts into mature homolog pairing. It has also been proposed that homolog pairing might start at the telomeres and proceed through the rest of the chromosome. But as we noted above, ho-

molog pairing is segmented in budding yeast, and pairing may give rise to topological knots [11].

Even outside the context of the bouquet, telomeres influence recombination. Subtelomeric regions of chromosome I show minimal recombination [16]. But meiotic ectopic repeat and allelic recombination rates on heterologous chromosomes show a negative correlation with distance from the telomere end. This negative correlation holds true hundreds of kilobases into the chromosome but does not depend on bouquet formation [9, 10]. These data argue for a telomere-based compartmentalization of the nucleus with specific roles in recombination regulation.

Important clues from the study of mutants in the *NDJ1* gene

Ndj1/Tam1 was the first telomere binding protein shown to be important for bouquet formation in synaptic organisms [7, 17]. *ndj1* mutants have delayed AE formation, defective homolog disjunction, delayed progression through meiotic prophase and defects in COI. The formation of bouquet and association to SPB is severely disrupted in *ndj1* nuclei [17]. Trelles-Sticken et al. [15] have proposed a role for Ndj1 in tethering telomeres to the SPB. Peoples-Holst and Burgess [18] have further suggested that by promoting the bouquet, Ndj1 facilitates homology search, thereby contributing to homolog alignment. One component of this is the delay in both CO and NCO formation and the twofold reduction of NCO products in *ndj1* mutants [18].

Ndj1 is also critical for meiotic telomere recombination. Telomere/telomere short tract homology recombination actually serves to reset elongated telomeres to wild-type lengths through single-step telomere rapid deletion (TRD) that are severely reduced in *ndj1*Δ mutants (Fig. 2) [19]. Whether this effect is telomere-specific is not yet known.

Structural factors in bouquet formation

Kar3 is a kinesin-like microtubule-dependent motor protein, needed for metaphase spindle formation [20] and for nuclear fusion in karyogamy. Haploid *kar3* mutants also carrying the mutation *spo13* that permits haploid meiosis I have normal centromere resolution, and unperturbed telomere bouquet formation and association to SPB. However, both the duration and persistence of bouquets were affected in these cells. These changes are likely to affect recombination since interhomolog recombination is reduced in this mutant.

The subset of actin that is present in the nucleus becomes a part of filaments attached to nuclear pore complexes that extend into the nucleus [21]. Blocking the polymerization of actin leads to rapid dispersion of clustered telomeres over the nuclear periphery [22]. Hence, nuclear

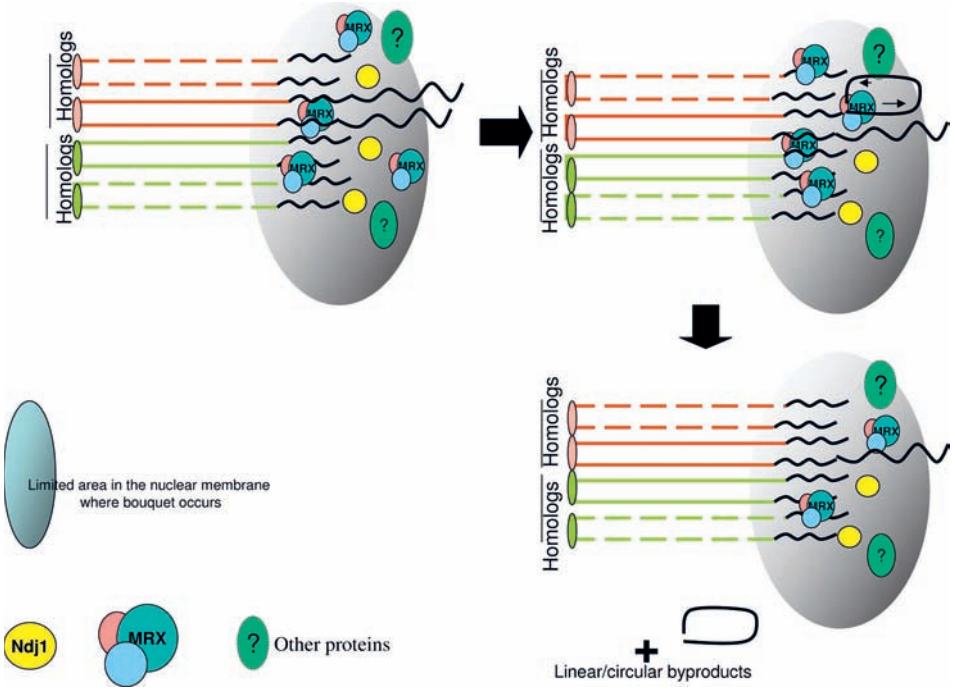

Figure 2. A model for telomeric recombination in budding yeast mediated by Ndj1. Ndj1 mediates bouquet formation, which in turn may cause an increase in local concentration of factors like MRX, leading to telomere recombination. The figure represents a situation where one of two elongated telomeres from sister chromatids deletes to the size of the majority of telomeres during meiosis.

actin has a critical role in maintaining the bouquet, possibly through interaction with the SPB.
Cohesin binding is essential for proper meiotic chromosome segregation in meiosis in a process that is mediated in part by Rec8, a component of the sister chromatid cohesion complex. While rec8Δ cells have a normal bouquet, the bouquet fails to disperse, unlinking the processes of formation and dispersion [22].

Cell cycle delays

The yeast protein Set1 is a histone methyltransferase that acts on histones H3 and H4 and is required in transcriptional silencing at telomeres. Deletion of *SET1* causes a delay of premeiotic S-phase [6]. Indeed, centromere resolution is greatly impeded with a limited dispersion of vegetative telomere clustering. Bouquets are never formed in *set1*Δ mutants.
The B-type cyclin, Clb5, is involved in premeiotic DNA replication. Deleting *CLB5* also delays premeiotic S-phase. The premeiotic DNA replication defect seen in *clb5*Δ does not affect centromere cluster resolution, but the dispersion of vegetative telomere clustering to the nuclear periphery is severely limited. Bouquets form but with significant delay. In contrast, bouquet structures are stable for an extended period [6].
Deletion of *IME2*, which also results in delayed premeiotic S-phase entry, confers a *clb5*Δ-like phenotype, displaying dissolution neither of centromeres nor of telomeres [6]. Together, these data argue for a tight control of the timing of telomeric bouquet formation in the transition from the vegetative to meiotic state.
In summary, telomere reorganization in the meiosis of *S. cerevisiae* is necessary for efficient meiotic recombination. The spatial constraint on chromosomes afforded by the bouquet may promote homolog pairing that in turn becomes necessary for strand-exchange intermediates promoted by DSBs. DSBs stabilize the pairing, and the SCs further fortify it. Alternate pathways may exist to localize and align homologs, resulting in the lack of an absolute requirement for the bouquet in meiotic recombination. Telomeres, on the other hand, may require intimate associations with one another for resetting telomere lengths (Fig. 2) [19, 23, 24]. In the absence of the bouquet, this sizing function may be lost.

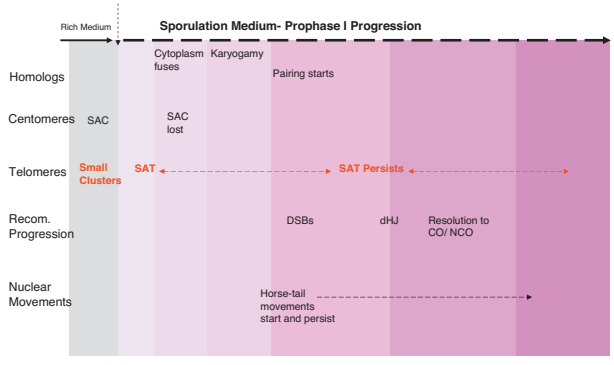

Figure 3. Timing of telomere clustering in relation to other meiotic events of *S. pombe.* Telomere clustering persists through most of prophase I. The approximate relative timings of recombination events are shown. The increase in background hue represents progression through meiosis. SAC, SPB-associated clusters; SAT, SPB-associated telomere clusters; CO/NCO, crossovers and non-crossovers; dHJ, double Holliday junctions.

Fission yeast

A more significant role for telomeres in meiotic recombination is observed in the fission yeast, *S. pombe*, with the formation of the dynamic horsetail configuration.
The mating of haploid cells and the subpopulation of diploids can undergo zygotic and azygotic meioses, respectively. Fission yeasts can undergo either zygotic or azygotic meiosis, initiating in haploid and diploid cells, respectively. Azygotic meiosis is similar, although not completely identical, to zygotic meiosis, with slightly reduced recombination frequencies in azygotic meioses [25]. We will focus on zygotic meioses below.
Haploid interphase cells of fission yeast exhibit the classic Rabl configuration of chromosome arrangement in the nucleus. In this orientation, telomeres are localized on the nuclear envelope, at several locations, in the orientation opposite to the SPB-centromere cluster [26]. Telomeres cluster to the SPB, probably driven by Spk1 and Mei2, kinases which drive cell conjugation. Centromeres are subsequently released from the SPB between cell conjugation and karyogamy, whereas the meiotic telomere clustering persists through prophase I [27].
Soon after karyogamy, the diploid nucleus begins an active phase of movement led by the SPB. These movements, called horsetail movements, are dramatic in fission yeast. The horsetail stage is maintained until the separation of chromosomes in prophase I [28]. Fission yeasts are asynaptic and do not form normal SC. As a consequence, they also lack COI, which prevents recombination events occurring in close proximity. In spite of the absence of synapsis, pairing and recombination occur efficiently [29]. Furthermore, pairing can occur through recombination and recombination-independent redundant mechanisms.
Recombination-independent mechanisms that contribute to homolog pairing include the telomere-clustering pathway. Mutations in the enzyme that forms most DSBs, *rec12*, abolish recombination without influencing horsetail movement or telomere clustering; pairing is not fully abrogated but occurs less efficiently [30].
Prolonged telomere clustering and the vigorous movements of the nucleus of fission yeast may compensate for the absence of synapsis to stabilize homolog interactions

and recombination. Telomere clustering spatially constrains the chromosomes, and horsetail movements may align chromosomes close in a limited space, increasing the possibility of homolog pairing [28]. In this context, telomere clustering may also prevent aberrant chromosomal interactions by spatial constraints. Proof of the importance of fission yeast telomeres in homolog pairing and recombination comes from FISH observations and greatly reduced recombination rates in clustering deficient and oscillation-deficient mutants.

Key proteins in telomere/meiotic relationships

Taz1 is the major telomere binding protein in *S. pombe* and regulates numerous aspects of telomere function, including telomere length regulation and silencing. Disruption of *taz1* leads to a majority of the cells with dispersed telomeres, many of which are not associated with the SPB and nuclear envelope [31]. In addition, *taz1*Δ cells have reduced homolog pairing and greatly reduced recombination frequencies. Intragenic recombination is reduced ~3.5 fold in taz1Δ cells compared with wild-type, while intergenic recombination drops from 22% to 2% [31, 32]. The recombination and pairing defects of *taz1*Δ could be due to the loss of telomere clustering.

Yeast two-hybrid assays show that Taz1 interacts with spRap1 [33]. Disruption of spRap1 also leads to disruption of clustering [33]. It has been proposed that the spRap1 associated with telomere-bound Taz1 promotes clustering, possibly through some intermediate factor. Thus, telomere clustering in these mutants could be defective because of their inability to associate with the SPB [33]. It is likely that sp-*rap*1^{-} cells will also have defective homolog pairing and recombination.

It has been suggested that a protein called Ccq1 that can bind to Taz1 and to an SPB component, Pcp1, serves as a critical bridge between SPB and telomeres. Indeed, reduction of ccq1+ gene dosage leads to the disruption of telomere clustering in meiotic prophase [34].

Kms1, an SPB component

Kms1 associates with another SPB protein, Sad1, and also with a microtubule motor dynein [35]. *kms1*– cells are not defective in mitosis. However, they are defective in karyogamy, and the SPB and telomeres are dispersed over the nuclear membrane. Telomeres remain attached to the SPB, and therefore telomere signals and SPB components are found to cosegregate even when they are fragmented across the nuclear membrane. *kms1*– cells show reduced homolog pairing. Intragenic recombination is reduced to 30–60% of wild-type levels. In addition, *kms1*– cells have reduced pairing in telomere proximal regions coupled with increased levels of ectopic recombination [35]. This argues for the roles of the bouquet and nuclear oscillation in restricting ectopic recombination in fission yeast.

Mei4

Other mutants that affect telomere clustering in *S. pombe* include members of four complementation groups, called *dot1*, *dot2*, *dot3* and *dot4*, that exhibit defects in telomere clustering [36]. One of these mutants, *dot4*, appears to be an allele of *mei4*+, a gene encoding a meiotic transcription factor, possibly inducing the telomere-clustering program.

The role of factors involved in heterochromatin formation

A possible target of Mei4, Rik1, is active in the formation of telomeric and centromeric heterochromatin and involved in telomere clustering [32]. Rik1's role in the formation of heterochromatin is mediated through Clr4-catalyzed methylation of histone H3. Interestingly, *clr4*Δ cells are also defective in telomere clustering. Telomere-SPB association in *rik1*– meiotic zygotes is disrupted to the same extent as in *taz1*– zygotes.

Yet another protein, a product of the *lot2* gene, which was isolated in a screen for mutations affecting telomere silencing, was found to affect telomere clustering in meiosis [37]. *lot2* mutant cells have also reduced pairing with recombination rates reduced 2.3-fold compared with wild-type. Taken together, these data argue for a role of silencing in meiotic telomere recombination.

Thus, proteins with diverse cellular functions – including heterochromatin formation, transcriptional regulation, SPB integrity, and telomere maintenance – have effects on telomere clustering and telomere-led horsetail movements. Defects in these proteins often lead to defects in recombination frequencies, underscoring the importance of clustering and movement in meiotic recombination.

In summary, fission yeast appears to have evolved a stronger dependency on their telomeres for recombination compared with budding yeast. The most straightforward explanation for this comes from the structural importance of telomeres in these two organisms. Since fission yeast lack SCs, the structural role in *S. pombe* may have shifted to the telomeres by clustering and horsetail movement, leading to the alignment of homologs. On the other hand, budding yeasts share the involvement of telomere clustering in homolog pairing, The effect of the bouquet structure formation is variable, possibly due to alternate pathways. However, recombination between telomeres in budding yeast seems to be completely dependent on bouquet formation. Although the bouquet was described more than a century ago, most of the molecular dependencies of the formation, dissolution and

relation to meiotic recombination have been dissected only in the past few years. For these ends, perhaps, this is just the beginning.

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