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Telomere attachment and clustering during meiosis

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Abstract. Telomeres are important segments of chromosomes that protect chromosome ends from nucleolytic degradation and fusion. At meiosis telomeres display an unprecedented behavior which involves their attachment and motility along the nuclear envelope. The movements become restricted to a limited nuclear sector during the so-called bouquet stage, which is widely conserved among species. Recent observations suggest that telomere clustering involves actin and/or microtubules, and is altered in the presence of impaired recombinogenic and chromosome related functions. This review aims to provide an overview of what is currently known about meiotic telomere attachment, dynamics and regulation in synaptic meiosis.

Keywords. Actin, bouquet, chromosome dynamics, nuclear envelope attachment, meiosis, pairing, telomere.

Introduction

Meiosis has evolved to compensate for the genome doubling that occurs at fertilization and to instigate genetic diversity in sexually reproducing eukaryotes. Two successive meiotic divisions, which lack an intervening DNA replication, halve the genome size to create the haploid chromosome number common to gametes or spores. A prerequisite for meiosis I division is the intimate pairing and reciprocal recombination between homologous chromosomes (homologues) during first meiotic prophase, which allows their segregation during the reductional meiosis I division [1].

Prophase I is classically subdivided into sub-stages according to consecutive changes in chromosome morphology [2]. After a single round of DNA replication, chromosomes become visible as thin threads and assemble protein cores along their length (axial elements, AEs) during the leptotene stage (or leptonema). AEs, which are made of specific cohesin, condensin and AE-specific proteins, become connected by transverse filament proteins during zygonema. This gives rise to a tripartite synaptonemal complex (SC) that encompasses all chromosomes in pachynema and is thought to regulate crossing over (for a review see [3]). The SC disassembles during diplonema, and as chromosomes condense, sites of crossing over become visible as chiasmata, which represent physical connections between non-sister chromatids. Monopolar attachment of sister kinetochores and loss of arm cohesion during anaphase I allow the segregation of homologues. The subsequent meiosis II division dissolves centromere cohesion and segregates sister chromatids (for review see [1, 4]).

Meiotic telomeres attach firmly to the nuclear envelope

In somatic mammalian cells telomeres are associated with a filamentous nuclear matrix and scattered throughout the nuclear volume [5–7]. When cells enter meiosis, premeiotic nuclear architecture is dissolved, telomeres reposition to the nuclear envelope (Fig. 1) and attach to the to the nucleoplasmic face of the inner nuclear membrane with the wide end of a conical thickening of the axial element end (Fig. 2) [8–10]. The telomere/nuclear envelope (NE) attachment is widely conserved across kingdoms and has been shown to resist pulling forces applied by micromanipulation or centrifugation [11, 12], suggesting that telomeres are tightly connected to some component of the cytoskeleton. Such a connection could be provided by filament bundles that project between the telomere attachment plate at the inner nuclear membrane through the NE to the cytoplasm (Fig. 2) ([13, 14] and references therein).

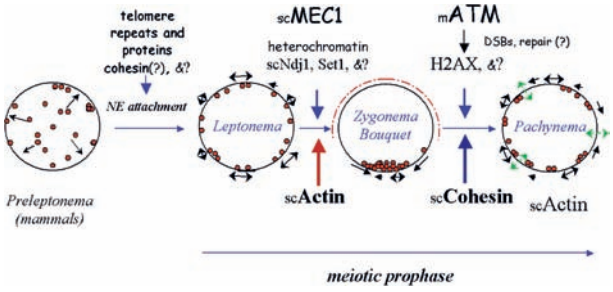

Figure 1. Proposed generalized scheme depicting the dynamics of meiotic telomere redistribution during synaptic prophase I. The mobility of telomeres is indicated by arrows. In the premeiotic nucleus (nuclear architecture of mammals and some plants depicted), telomeres (red) are scattered in the nuclear lumen. Induction of meiosis leads to movement of telomeres to the NE (arrows) in maize and mammals. In budding yeast, telomeres disperse from a few perinuclear clusters after premeiotic replication. Attachment requires telomere repeats and likely a meiotic telomere protein complex that contains proteins such as scNdj1 and TRF2. During leptonema NE-attached telomeres carry out undirected long-range movements over the NE (arrows). Drug experiments in *S. cerevisiae* suggest that actin polymerization (red half-circle) mediates telomere clustering in early zygonema (bouquet stage) by restricting telomere movements to the cluster site, which is defined by the MTOC (animals, fungi). At pachynema telomeres are motile and scattered while additional nuclear deformations and rotations occur (green arrows). In the presence of compromised telomeric heterochromatin (*set1*Δ), the scMec1 kinase prevents bouquet stage formation (see text), while exit from the bouquet stage is dependent on functional cohesin. In mouse meiosis the ATM kinase and its downstream effector H2AX promote bouquet stage exit, implying a role of chromatin structure and/or recombinogenic DSB repair in the regulation of telomere cluster resolution. The latter is underlined by extended telomere clustering in recombination-deficient mutants of *Sordaria*, yeast and mouse. For details see [28, 58, 87–89].

Bouquet formation

During the leptotene/zygotene transition, NE-attached telomeres somehow move along the inner nuclear membrane to transiently cluster adjacent to the cytoplasmic microtubule organizing center (MTOC) of animals and fungi [15]. In plants, which lack a localized MTOC, telomere clustering occurs at the microtubule-poor cell cortex [16]. In *Caenorhabditis elegans* or coccids (intracellular parasites) telomere clustering involves only one end per chromosome [17, 18]. The nuclear topology of the bouquet stage in synaptic meiosis is usually observed for a limited period of prophase I which comprises the leptotene/zygotene transition (reviewed in [19]), while it persists for much of prophase I in the asynaptic meiosis of *Schizosaccharomyces pombe* [20, 21]. In *Arabidopsis*, meiotic telomere clustering establishes prior to entry in prophase I at the nucleolus and is relaxed during leptotene when recombination is initiated [22].

Cohesin and meiotic telomere function

Sister chromatid cohesion (SCC) at meiosis is important to instigate recombination between non-sister chromatids and for chromosome segregation at meiosis I and II [23]. Interestingly, meiotic *Saccharomyces cerevisiae* telomeres lacking the Ndj1/Tam1 protein display defective SSC [24, 25] and are compromised in telomere peripheralization [26], which poses the question whether telomere adhesion to the NE involves cohesin function. Cohesin is a protein complex that is required for morphogenesis of meiotic chromosome cores and homologue segregation (for review see [1, 4]). Mice lacking the AE protein SYCP3 lack AEs [27] but assemble cohesin cores and undergo sister telomere cohesion, attachment and bouquet formation [14]. Similarly, yeast meiocytes lacking the AE protein scRed1 undergo telomere clustering and, by inference, NE attachment [28], suggesting that AE formation is dispensable for meiotic telomere/NE attachment.
However, mice lacking the meiosis-specific cohesin subunit SMC1β exhibit a subset of zygotene/pachytene telomeres in the nuclear lumen, suggesting that meiotic cohesin or SMC1β function is required for faithful telomere/NE attachment [29]. It remains to be determined whether *Smc1*$\beta^{-/-}$ telomeres fail in attachment or whether some telomeres lose attachment. Absence of the scREC8 cohesin [30] inhibits exit from telomere clustering and disrupts spindle pole body (SPB)/telomere cluster colocalization [28]. Ectopic expression of the mitotic cohesin SCC1 in *rec8*Δ meiosis rescued these defects, indicating that cohesin mediates telomere cluster/MTOC colocalization and exit from the bouquet stage, at least in budding yeast meiosis. It will be interesting to investigate the ultrastructure of cohesin-deficient telomeres in *S. cerevisiae* and to learn about telomere dynamics in other cohesin-deficient models.

Meiosis and telomere attachment requires telomere repeats and proteins

Interference with telomere structure in yeasts, mouse and worm model organisms by e.g. manipulation of telomerase activity or specificity has revealed that loss of telomeric repeats compromises passage through meiosis [31–35]. Meiocytes of female generation 4 *Terc*$^{-/-}$ mice display reduced telomere repeat tracks and experience defects in AE formation and synapsis [33]. This is probably due to a less stringent prophase I control in female meiosis and suggests a role for telomeres in mediating AE formation and synaptic pairing. Mammalian ring chromosomes without telomere repeats fail to localize to the nuclear periphery of spermatocytes [36], while maize ring chromosomes with telomere repeats at the fusion site participate in meiotic telomere attachment and clus-

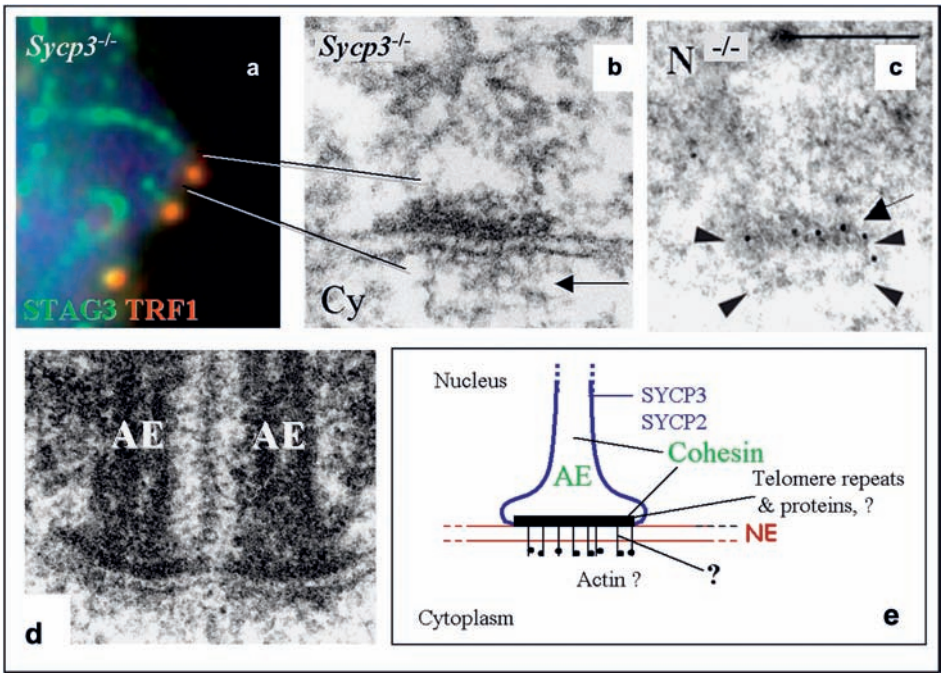

Figure 2. Meiotic telomere attachment. (*a*) Sector of a *Sycp3*$^{-/-}$ zygotene-like mouse spermatocyte nucleus showing rugged cohesin cores (green, STAG3 cohesin subunit) and telomeres (TRF2, red) at the nuclear periphery. Telomere signals appear orange due to Stag3/telomere signal colocalization. (*b*) Electron micrograph (EM) section of a telomere attachment of a *Sycp3*$^{-/-}$ spermatocyte showing a dark electron-dense attachment plate at the nucleoplasmic face of the nuclear membrane (nucleus is at the top), from which fibrillar material traverses the nuclear envelope (NE) and extends into the cytoplasm (Cy; arrow). Note the absence of AEs in this condition. (*c*) EM in situ hybridization with a T_2AG_3 repeat probe reveals telomere repeat signals (black dots represent gold grains) confined to the attachment plate at the nucleoplasmic face of the NE (upper arrowheads). N, nucleus. (*d*) (NE) Attachment of an SC of a wild-type mouse spermatocyte shows dark axial elements (AE) emanating from their attachment plates into the nucleoplasm in the upper part of the image. (*e*) Scheme depicting components of the meiotic telomere/nuclear envelope attachment. The telomere makes contact with the nucleoplasmic face of the NE through a dark electron-dense plate (black bar). Genetic and immunoflurorescence data suggest that the attachment plate contains telomere repeats and telomere proteins like TRFs, cohesin subunits and the AE protein SYCP2. The latter two are also found in the AE, while SYCP3 is specific to the AE. The nature of the fibers traversing the nuclear envelope remains to be determined. As inhibition of actin polymerization prevents or dissolves telomere clustering, it may be speculated that actin (dots) could act on these fibers on the cytoplasmic side of the attachments to drive their clustering. *b*, *c*, *d* reproduced from [14]; bar for *c* and *d*, 0.2 µm.

tering [37], suggesting that telomere repeats contribute to NE attachment, raising the question how this is mediated.

Similarly to somatic cells [38] telomeres of meiocytes have been found to contain duplex $(T_2AG_3)_n$ repeat-binding proteins: in mammals TRF1 and TRF2 and interacting proteins Rap1, Tin2, tankyrase1 as well as the homologous recombination proteins Nbs1 and Mre11 [14, 39, 40]. Nuclear envelopes of frog oocytes contain a TRF2 homologue [41]. In fission yeast meiosis telomere attachment and clustering at the SPB depends on the presence of the telomere proteins Taz1 and spRap1 at the chromosome end [42, 43]. *S. cerevisiae* telomere repeats bind scRap1 in mitosis and meiosis [44, 45], while at meiosis telomeres additionally integrate the telomere protein Ndj1/Tam1 [24–26]. scRap1 has been found crucial for progression through meiosis, as strains with altered telomere sequence or scRap1-binding sites experience defective meiosis [31, 46]. Ndj1-deficient cells undergo meiosis with a delay, display reduced levels of recombination and homologue disjunction [24, 25], and fail to undergo telomere peripheralization and clustering [26].

High throughput data suggest that Ndj1 interacts with the SPB component Msp3, which interacts with the telomere-associated protein Est1 [47]. It remains to be determined whether Ndj1/Msp3 interactions play a role in telomere tethering at the NE-bound SPB. It has been suggested that the protein complex that links telomeres and the spindle pole body (the fungal microtubule-organizing center) involves the SMC protein Ccp1 and the pericentrin Pcp1p [49–52]. More recently, it was observed that the meiosis-specific expressed proteins Bqt1 and Bqt2 connect telomeres to the Sad1 spindle pole body protein [53]. In fission yeast meiosis, ring chromosomes of *S. pombe* that form a telomere protein complex at the chromatin of the fusion site participate in meiotic telomere clustering [48]. Together the observations above suggest that telomere/NE attachment requires the assembly of a meiosis-specific telomeric protein complex.

Heterochromatin is required for meiotic telomere clustering

A special feature of telomeric heterochromatin seems to regulate telomere clustering in meiosis, since *S. pombe* meiocytes that lack Rik1 and the chromo- and SET-domain Clr4 histone methyltransferase fail in meiotic telomere clustering at the SPB [54]. In budding yeast, the Set1 histone H3-K4 methyltransferase [55, 56], which contributes to heterochromatin formation, telomere silencing, recombination and meiotic gene expression [57], is required for telomere clustering but not for telomere attachment [58]. Since telomere clustering occurs in absence of the Sir3 protein [59], a component of repressive telomeric chromatin [60], it is possible that a checkpoint prevents telomere clustering in Set1-deficient meiosis. It will thus be important to further dissect the interplay between telomere clustering and chromatin structure (see below). Telomere capping function can be separated from attachment in the meiosis of mice double null for the *Suv39h1* and *Suv39h2* histone H3 methyltransferases, where telomere fusions occur in the presence of bouquet formation ([61], H. S., T. Jenuwein, unpublished data). Highlighting that proper function of the telomeric chromatin domain prevents illegitimate exchange events between meiotic chromosome ends. How this is regulated remains to be worked out.

Proteins of the nuclear envelope and attachment

So far, information about the protein(s) that mediate telomere/NE attachment in synaptic meiosis is scarce. In somatic cells the nuclear periphery and envelope are linked to the actin and microtubule cytoskeleton via nesprin, SUN and lamin protein family members (for review see [62, 63]). Whether these proteins play a role in telomere attachment in prophase I remains to be investigated. Interestingly, male mice lacking the A-type lamin isoform C2 fail to complete meiosis, have chromosome pairing defects but undergo fine meiotic telomere/NE attachment and clustering [64], suggesting a role for A-type lamins in promoting chromosome dynamics and prophase I progression in spermatogenesis. Similarly, mice deficient for the LAP2β associated protein Mgcl-1 [65] also undergo meiotic telomere/NE attachment and clustering [66], leaving the quest open for nuclear envelope components that play a role in meiotic telomere attachment.

Microtubule-dependent telomere mobility during prophase I

Nuclear and chromatin mobility has been observed in live leptotene and zygotene meiocytes of insects [67] and mammals [68]. In the latter they were found to be sensitive to colcemid, a colchicine derivative that dissociates microtubules (MTs) and damages the meiotic nuclear envelope [69]. Inhibition of telomere clustering in rye anther cultures occurs at colchicine concentrations that fail to disrupt cytoplasmic MTs [70]. Thus, it remains to be seen whether the colchicine-mediated clustering defect is due to a deleterious effect of this drug on the meiotic nuclear envelope, which has been observed in mouse [69]. The sweeping nuclear movements that are led by the SPB/telomere cluster along cytoplasmic microtubules in live *S. pombe* meiocytes [71, 72] are dependent on MTs, the dynein heavy-chain motor protein Dhc1 and the dynein light-chain-family protein Dlc1 [51]. In budding yeast meiosis, MT disruption only moderately reduces meiotic telomere clustering [28], while the latter is increased in the absence of the minus-end kinesin scKar3 [59]. The observations above suggest that MT-dependent processes contribute to meiotic nuclear motility and telomere clustering, the extent of which may vary among species.

Actin drives telomere and nuclear motility in *S. cerevisiae* meiosis

Meiotic telomere, clustering, and nuclear deformations and rotations have been found to depend on actin polymerization [28], suggesting actin-based mechanisms to be the major driving force behind nuclear and telomere movements in budding yeast meiosis. Leptotene telomeres seem to undergo undirected, long-range undirected movements along the nuclear periphery of wild-type or ATP-depleted meiocytes [C. Adelfalk and H. S., unpublished]. Actin can form short branched filaments, which are thought to be effective motors in the range of 100–150 nm [73, 74]. In yeast bouquet meiocytes actin immunostaining revealed F-actin patches and granular signals in the cytoplasm [C. Adelfalk and H. S., unpublished]. Since inhibition of actin polymerization releases telomeres from the cluster site [28], it is hypothesized that actin polymerization into short, branched filaments excludes motile telomeres gradually from much of the NE area, thereby herding them up at the cluster site. It will be important to determine whether cytoplasmic and/or nuclear actin contribute to telomere clustering. If cytoplasmic actin should act on the telomere attachment at the NE, it may do so on the fibrillar extensions that emanate into the cytoplasm opposite to telomere attachments (see above; Fig. 2b). Nuclear actin, on the other hand, which associates with chromatin remodeling and transcriptional complexes and the nuclear lamina (reviewed by [62, 75]) could play a role in movements of intranuclear telomeres to the NE that occur during mammalian preleptotene. Since actin drug treatment only affects nuclear and telomere mobility in meiotic cells [28, 76], it will be interest-

ing to learn about its regulation and the interplay with cohesin-dependent processes, and to study the actin network of the meiocyte at a high resolution. Whether actin plays a role in meiotic telomere clustering in other organisms is also a challenging question, as is how the microtubule cytoskeleton aids actin-driven telomere clustering.

Meiotic telomeres facilitate homologue search

The phenotype of bouquet mutants supports the long-held view that telomere clustering facilitates homologue pairing: homologue pairing is significantly delayed in meiosis of the *ndj1*Δ bouquet mutant of *S. cerevisiae* [26] or when bouquet formation is inhibited by actin drugs [28]. Furthermore, increased ectopic recombination interactions in bouquet-less fission and budding yeast meiosis indicate that telomere clustering reduces the complexity of homology searching [77, 78]. In *S. pombe* meiosis full levels of recombination and homologous associations along chromosome arms depend on telomere clustering, while nuclear motility mediates pairing of centromere regions [79]. Regional differences in the efficacy of stable homologue pairing were also noted in synaptic *S. cerevisiae* meiosis [80]. It will be interesting to learn about homologue interactions and recombination in actin-depleted synaptic meiosis which lacks both telomere clustering and nuclear motility.
Telomere clustering endures in *S. cerevisiae rec8*Δ*spo11*Δ meiosis that lacks DNA double-strand breaks (DSBs) due to absence of Spo11, which forms the programmed DSBs that initiate recombination (for review see [81]). In this condition chromosome pairing fails [28], which highlights the importance of DSBs for homology recognition [82]. Telomere clustering plays only a supportive role in this process, likely by boosting chromatin interactions [83].

Telomere clustering is controlled at several levels

If bouquet formation instigates homology recognition, it will be attractive for the cell to coordinate the appearance of telomere clustering and DSBs. Insights into such regulation come from mutant conditions. Meiosis in humans and mice fails in the absence of the ATM kinase, which is central to the somatic DNA damage surveillance machinery [84]. Besides other defects, meiotic chromosomes of $Atm^{-/-}$ mice experience fragmentation [85] and display extended telomere clustering [86, 87]. Reduced bouquet frequencies in $Atm^{-/-}Spo11^{-/-}$ mice [66] and *Spo11* and *rad50S* mutants of *Sordaria* and yeast suggest that telomere clustering persists if DSBs fail to form or are left unrepaired [88, 89]. Since ATM has been found to physically interact with TRF2 [90], it is possible that ATM plays a direct role in meiotic telomere mobility. Ectopic and meiotic DSBs induce ATM to phosphorylate, among other targets, histone H2AX at Ser-139 [91, 92]. H2AX-deficient mice also feature elevated bouquet frequencies [93], suggesting a link between chromatin state and the regulation of telomere clustering. In budding yeast meiosis the Mec1 kinase prevents bouquet formation when telomeric heterochromatin is compromised [58]. Since Mec1 is homologous to the mammalian ATM-related, ATR kinase, it will be interesting to determine the role of ATR in regulation of meiotic telomere dynamics. In some mutant conditions persistence of the bouquet stage seems to result from an overall slowed transition through prophase I [88]. In mammals, bouquet stage extension occurs in the female sex [94] and coincides with altered progression of recombinational repair, despite a similar prophase I duration in the two genders [95]. It is possible that the cell strives to restrict chromosome movements through telomere clustering during a time when DSBs are formed and processed, which also provides a unique opportunity for homology sensing and for resetting telomere length among clustered chromosome ends by telomere rapid deletion [96].

Conclusions

In summary, it appears that in the majority of sexually reproducing species meiotic telomere/nuclear envelope attachment paves the way for prophase I movements that promote physical interactions between chromosomes and telomeres during the bouquet stage, which likely reduces the complexity of homologue search. It seems plausible that meiotic chromosome cores and their NE attachment have evolved to stabilize the relaxed chromatin of meiotic chromosomes when these carry DSBs and undergo extensive movements. Since these features improve the fidelity of meiosis and inheritance, it will be interesting to further dissect the pathway(s) that converge on meiotic telomeres.

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