RESEARCH UPDATE

Role of telomeres and centromeres in meiotic chromosome pairing

Meiosis is a process in which haploid cells are produced from diploid parent cells after two successive rounds of nuclear division. During the first division of meiosis, homologous chromosomes segregate to opposite poles of the dividing cell. Chromosome mis-segregation results in the eventual formation of aneuploid gametes, which may cause fertility problems and chromosomal abnormalities in the offspring, such as Down syndrome in humans.

Homologous chromosome pairing

To ensure correct chromosome segregation, homologous chromosomes must pair and synapse during an early stage of meiosis I, known as meiotic prophase. During chromosome pairing, two homologous chromosomes (one paternal and one maternal) recognize each other and align, forming a close physical association. The mechanisms of chromosome pairing remains poorly understood. Pairing is closely followed by synapsis, which is a process of installation of a proteinaceous structure, the synaptonemal complex, between the two paired chromosomes. Synapsis stabilizes the pairing interaction. However, by itself, synapsis does not require proper pairing. In pairing-defective mutants, the synaptonemal complex can be installed between nonhomologous chromosomes.

In most organisms, proper homologous chromosome pairing requires formation of DNA double-strand breaks (DSBs) in chromosomal DNA catalyzed by a topoisomerase-like protein, SPO11, which is essential for the initiation of meiotic recombination. However, the DSB dependence of pairing and synapsis is not universal. In *Caenorhabditis elegans* (a small nematode worm) and *Drosophila melanogaster* (the fruit fly), chromosomes pair and synapse normally in the absence of DSB formation, suggesting that chromosome pairing in these species is controlled by a different mechanism. However, in all species surveyed, there is good evidence that chromosome dynamics play a critical role in homologous pairing. In most species, chromosome ends (telomeres) exhibit particular behavior, known as telomere bouquet formation, which facilitates chromosome alignment and pairing. In a few species, it also has been shown that chromosome centromeres (sites on chromosomes by which they attach to the spindle during cell division) are actively involved in chromosome pairing.

Telomere bouquet

At the beginning of meiosis, the telomeres of all chromosomes in most species of plants, animals, and fungi attach to the nuclear envelope and cluster, which leads to formation of the telomere bouquet (**Fig. 1**). Mutants defective in bouquet formation also show defects in homologous chromosome pairing. Although chromosomes in these mutants do pair in many cases, pairing is slow and inefficient. Consequently, it has been generally believed that telomere clustering facilitates homologous pairing by bringing chromosome ends together.

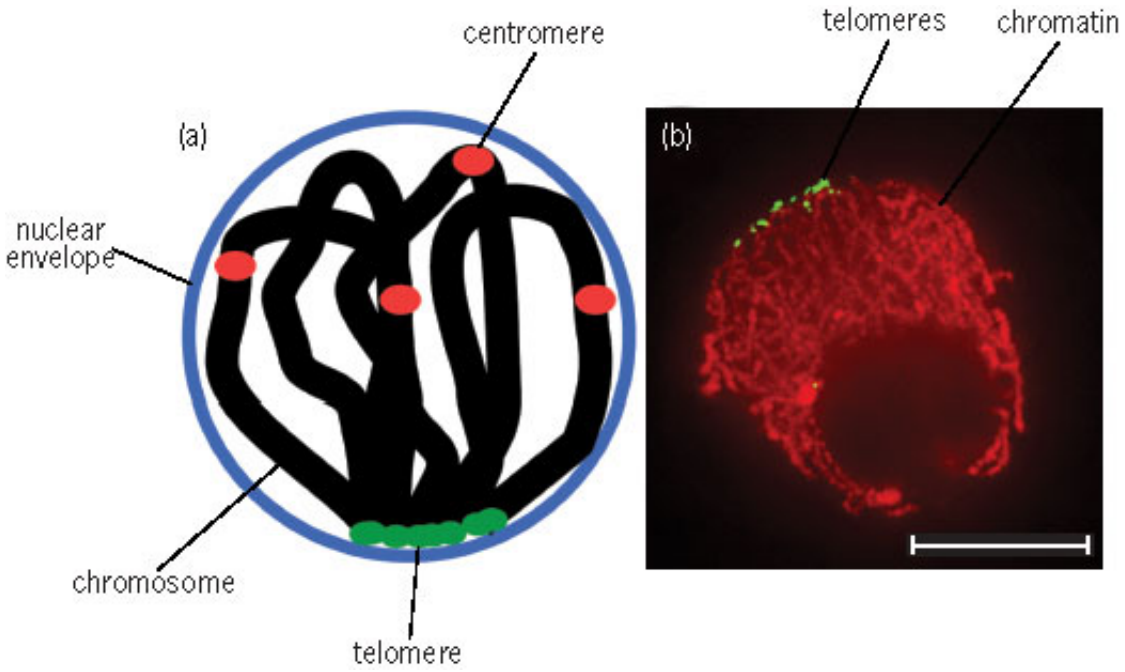

Fig. 1 (*a*) A diagram of the telomere bouquet. The telomeres of all chromosomes are clustered on the nuclear envelope. Centromeres are also shown. (*b*) The telomere bouquet in a wild-type maize nucleus during meiotic prophase. The telomeres and chromatin are indicated. (*Image courtesy of M. Sheehan; adapted from A. Ronceret and W. P. Pawlowski, Chromosome dynamics in meiotic prophase I in plants*, *Cytogenet. Genome Res., 129:173–183, 2010*)

Bouquet formation has not been observed in some organisms, including *Arabidopsis thaliana* (thale cress) and *C. elegans*. In *C. elegans*, telomeres attach to the nuclear envelope during early prophase I, but do not cluster. In *Arabidopsis*, telomeres cluster during interphase and at the beginning of meiotic prophase on the nucleolus rather than on the nuclear envelope. Telomeres of homologous chromosomes pair at the beginning of meiosis and dissociate from the nucleolus without forming the typical bouquet. However, during early meiotic prophase, telomeres become associated with the nuclear envelope and occasionally exhibit loose clustering. Overall, although a bona-fide bouquet is not formed in *Arabidopsis* or *C. elegans*, some features of the bouquet formation process, such as telomere attachment to the nuclear envelope, are present. These remnant features might play roles similar to the role of the bouquet in facilitating chromosome pairing.

Telomere–nuclear envelope attachment and telo-mere dynamics

Studies in several species, particularly fission yeast, have led to identification of a number of proteins involved in telomere attachment to the nuclear envelope (**Fig. 2**) and bouquet formation. In fission yeast, the Taz1 protein, which acts to maintain the proper copy number of telomeric repeats, has been shown to be required for bouquet formation. This protein interacts with three other telomere-associated proteins: Rap1, Bqt1, and Bqt2. The Rap1/Bqt1/Bqt2 protein complex forms a link between the telomeres and Sad1, a transmembrane protein located in the inner membrane of the nuclear envelope. Sad1 homologs have been identified in a number of diverse species, including budding yeast, mice, *C. elegans*, *Drosophila*, *Arabidopsis*, and maize. They are distinguished by the presence of an evolutionarily conserved SUN domain. Sad1 binds another transmembrane protein, Kms1, which is located in the outer membrane of the nuclear envelope and which interacts on its cytoplasmic end with the cytoskeleton and cytoskeletal motor proteins. Kms1

homologs have been also identified in many species, such as *Drosophila, C. elegans*, and mammals, and are collectively known as KASH proteins. The SUN/KASH protein pairs function in meiosis by linking chromosome ends with the cytoplasmic cytoskeleton (Fig. 2). The two proteins also function outside of meiosis, and their exact roles are still not well understood.

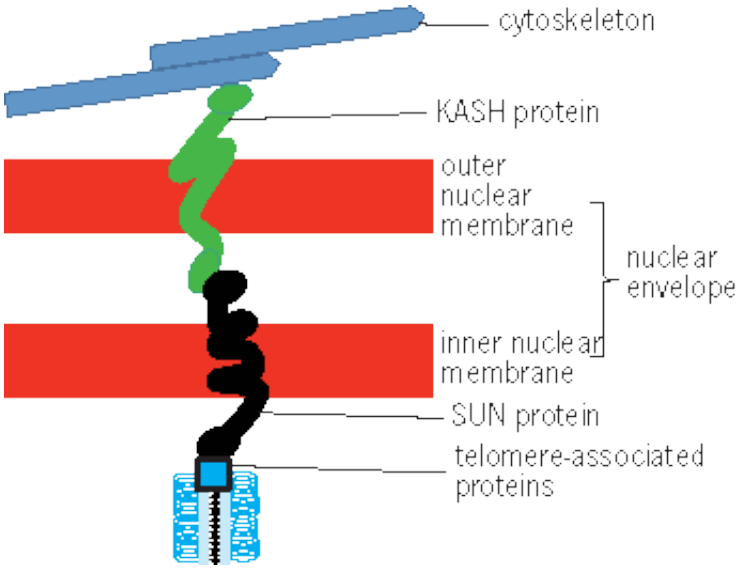

Fig. 2 A diagram showing the telomere–nuclear envelope attachment. Telomeres connect to the nuclear envelope through a telomere-associated and a SUN domain proteins. The SUN domain protein in the lumen of the nuclear envelope interacts with a KASH protein, which also interacts with the cytoplasmic cytoskeleton.

In a number of species, including budding and fission yeasts, rats, mice, *C. elegans*, and maize, it has been observed that chromosomes exhibit dynamic and complex movements during early stages of meiotic prophase. These movements are particularly dramatic in fission yeast, where they are known as “horse-tail” movements, in which the entire nucleus moves violently back and forth. In maize, several types of meiotic prophase chromosome movements have been observed. Rapid short-distance movements of fairly small chromosome segments adjacent to the telomeres coincide with chromosome pairing. At the same time, interstitial chromosome segments exhibit more restrained motility. After pairing is completed, these movements are supplanted by movements of much longer chromosome segments (sometimes entire chromosome arms) that exhibit slow, sweeping motions across large extents of the nucleus. In addition to the movements of individual chromosome segments, the entire chromatin exhibits oscillating rotations, often by as much as 90^{o}. The rotational movements are present both during chromosome pairing and also after pairing is completed. The earlier, pairing-associated movements may facilitate chromosome homology recognition by allowing many pairing combinations to be tried until a proper homologous interaction is found. The later, slower movements may help to resolve chromosome entanglements that remain after the conclusion of chromosome pairing.

Meiotic prophase chromosome movements rely on the attachment of chromosome ends to the nuclear envelope, and forces generated in the cytoskeleton are necessary for the movements to occur. In budding yeast, cytoplasmic actin cables have been implicated in facilitating chromosome motility. In fission yeast, *C. elegans*, and rats, microtubules are involved. In maize, chromosome movements require both actin and tubulin.

Observations of the vigorous chromosome motility in early meiotic prophase and examinations of the role that these movements may play in chromosome pairing in several species, including *C. elegans*, which lacks the bouquet, shed a

new light on the function of the bouquet. It is likely that the bouquet's main role is providing chromosome attachment to the nuclear envelope and transmitting forces that generate chromosome movements, rather than just bringing chromosome ends together.

Role of centromeres in chromosome pairing

In contrast to telomeres, much less is known about the role of centromeres in chromosome pairing. In some organisms with relatively large genomes, centromeres cluster opposite telomeres in interphase cells and at the onset of meiosis. This arrangement is called Rabl orientation (**Fig. 3**). The presence of Rabl may provide a role for centromeres in chromosome pairing. In tetraploid and hexaploid wheat, the centromere clustering is regulated by the *Ph1* locus. The functions of *Ph1* are to reduce association of nonhomologous centromeres and promote association of centromeres of homologous chromosomes. However, the *Ph1* locus does not affect telomere clustering or pairing of chromosome ends, suggesting that centromere pairing is independent of pairing of other chromosome regions.

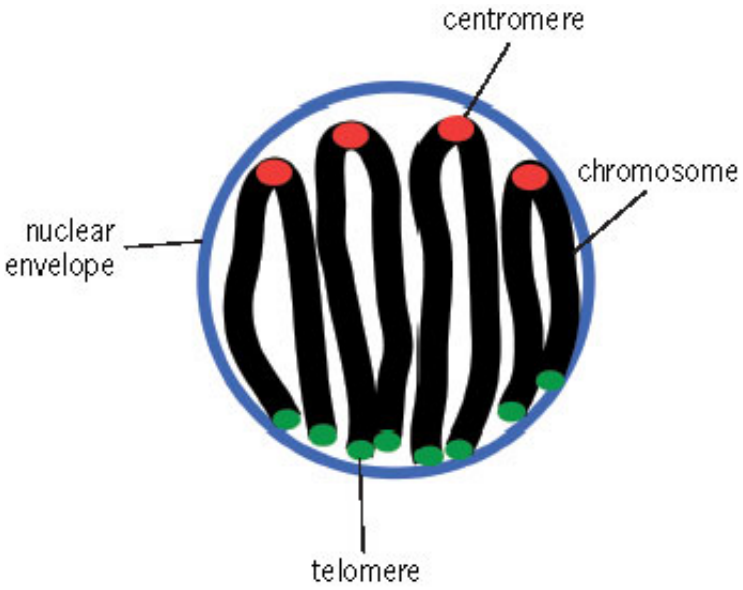

Fig. 3 A diagram of Rabl orientation. Centromeres of all chromosomes are located on the opposite side of the nucleus away from the telomeres. The nuclear envelope is also shown. (*Adapted from W. P. Pawlowski, Nuclear organization and dynamics in plants, Curr. Opin. Plant Biol., 13:640–645, 2010*)

Centromere associations that precede pairing of chromosome arms have also been described in budding yeast, a species with a relatively small genome that does not exhibit Rabl orientation. These associations are initially formed between nonhomologous centromeres but are converted to associations of centromeres of homologous chromosomes at the onset of chromosome pairing by a mechanism that depends on SPO11. Both nonhomologous and homologous centromere associations require installation of synaptonemal complex proteins in the centromere region. As observed in wheat, centromere associations in yeast are independent of the telomere bouquet formation. However, in contrast to wheat, chromosome arm pairing in yeast depends on the initial pairing at the centromere.

Conclusions

There are three main conclusions: (1) During early meiotic prophase, telomeres of all chromosomes attach on the

nuclear envelope. In most species, the nuclear envelope attachment is followed by telomere clustering, known as telomere bouquet formation, which brings chromosome ends into close proximity. This configuration may aid chromosome interactions. (2) A SUN/KASH domain protein complex connects chromosome ends to the cytoplasmic cytoskeleton, which is essential for promoting chromosome movement. Telomere-led chromosome motility during early prophase I facilitates chromosome pairing. (3) In some species, such as budding yeast and polyploid wheat, chromosome pairing is promoted by centromere associations that precede pairing along chromosome arms. Centromere pairing is independent of both telo-mere bouquet formation and pairing of chromosome ends.

See also: Cell biology; Cell cycle; Cell division; Cell motility; Cell nucleus; Chromosome; Chromosome aberration; Cytoskeleton; Genetics; Meiosis; Protein

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Additional Readings

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