Pairing of homologous chromosome is a unique event in meiosis that is essential for both haploidization of the genome and genetic recombination. Rapid chromosome movements during meiotic prophase are a key feature of the pairing process. This is usually telomere-led, and in metazoans is dependent upon microtubules and dynein. Chromosome movements culminate in the formation of a meiotic "bouquet" in which nuclear envelope-associated telomeres are clustered at the centrosomal pole of the nucleus. Bouquet formation is thought to facilitate homolog pairing. Recent studies reveal that coupling of telomeres to cytoplasmic dynein is mediated by SUN1 in the inner nuclear membrane (INM) and KASH5 a novel protein of the outer nuclear membrane (ONM). Together SUN1 and KASH5 assemble to form a transluminal LINC (linker of the nucleoskeleton and cytoskeleton) complex that spans both nuclear membranes. SUN1 forms attachment sites for telomeres at the INM while KASH5 functions as a dynein adaptor at the ONM. In mice deficient in KASH5, homologous chromosome pairing does not occur. The result is that meiosis is arrested at the leptotene/zygotene stage of meiotic prophase 1, and as a consequence both male and female mice are infertile. This study demonstrates an essential role for dynein directed telomere movement during meiotic prophase.

Introduction

The evolution and diversification of eukaryotes has, to a large extent, been facilitated by sexual reproduction. The mixing and subsequent shuffling of genes between generations provides the raw material upon which natural selection can act. Sexual life cycles are underpinned by the process of meiosis, in which parental homologous chromosomes are segregated, in a reduction division, to yield haploid cells. In higher eukaryotes, meiosis is a crucial step in the development of mature germ cells, and the evolution of meiosis has been a topic of considerable debate. While there is little doubt that meiosis represents a modified form of mitosis, it features several unique steps. These include the pairing of homologous chromosomes coupled with widespread recombination between non-sister chromatids. Following homolog segregation, a second mitosis-like division distributes non-replicated chromatids between daughter cells.

The first meiotic prophase (prophase 1) is characterized by the pairing of homologous chromosomes and the assembly of synaptonemal complexes. The latter are specialized structures resembling molecular zippers extending the entire length of each chromosome and which hold the homologs together. The mechanism by which homolog pairs are established during meiotic prophase has been a topic of considerable debate. The missing LINC A mammalian KASH-domain protein coupling meiotic chromosomes to the cytoskeleton

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The double membrane architecture of the NE raises the question of how chromosomal regions, telomers in particular, can be physically linked to the cytoskeleton during meiotic prophase 1. Since the NE remains intact during the process of synopsis there has to be molecular machinery in place that spans both the INM and ONM that can interact with cytoskeletal components and with chromatin. A possible solution to this puzzle was provided by studies on interphase somatic cells. These revealed that nuclear structures, including nuclear lamins, are mechanically coupled to a variety of cytoskeletal proteins.40-43 The nature of this coupling is partly dependent on two families of integral nuclear membrane proteins: SUN (Sad1, Unc-84) domain proteins, which reside in the INM, and KASH (Klarsicht, Ankyrin, and Syne Homology) domain proteins, residing in the ONM.44-47 KASH domain proteins play important roles in nuclear migration and positioning in a variety of cell and tissue types in multiple organisms, and interact with an assortment of cytoskeletal components. For instance, both Nesprins 1 (Nesp1) and 2 (Nesp2) represent ONM adaptors for cytoplasmic dynein in meiotic cells.

Figure 1. Comparison of mammalian KASH-domain proteins.48-50 In all cases the N-terminal domain resides within the cytoplasm while the C-terminal KASH domain extends across the outer nuclear membrane (ONM) and into the perinuclear space (PNS) where it interacts directly with members of the SUN domain protein family. The largest isoforms of nesprins 1 and 2 (Nesp1 and Nesp2) feature an N-terminal actin binding domain. These proteins also possess kinesin and dynein binding functions. In the case of Nesp2, the kinesin binding region resides close to the KASH domain since a smaller Nesp2 isoform, Nesp2β, is capable of recruiting kinesin to the nuclear envelope.49 One other vertebrate KASH domain protein, Nesp4 also functions in kinesin binding. Nesp4 is expressed largely in epithelial cells where it might have a role in nuclear positioning. Nesp3 functions as an adaptor for plectin, a versatile cytolinker molecule that provides a means of coupling nuclei to the intermediate filament system.64 Plectin binding is essential for cytoplasmic dynein binding functions.65 Nesp3 functions as an ONM adaptor for cytoplasmic dynein in meiotic cells.

The general structure of the NE has been conserved in all eukaryotes.51 Its most prominent features are the inner and outer nuclear membranes (INM and ONM) separated by a perinuclear space (PNS) of about 50 nm. The two nuclear membranes are periodically connected at annular junctions where they are spanned by nuclear pore complexes, massive multi-protein assemblies mediating the to-and-fro movement of macromolecules between the nucleus and cytoplasm. However, despite these connections, the INM and ONM are biochemically distinct. The INM contains a unique array of 60 or more integral membrane proteins13 and is associated on its nuclear face with the nuclear lamina, a thin (10–50 nm) relatively insoluble protein meshwork. The nuclear lamina is composed primarily of A- and B-type lamins,14 prototype members of the intermediate filament protein family. In addition to its interactions with the INM, which is mediated by several integral proteins, the lamina provides anchoring sites at the nuclear periphery for underlying chromatin domains and is thought to represent an important structural determinant for the NE as a whole. The ONM, on the other hand, is functionally related to the peripheral endoplasmic reticulum (ER), with which it maintains numerous connections. In this way, the ER, ONM, and INM may be considered as separate domains within a single continuous membrane system with the PNS representing a perinuclear extension of the ER lumen.
by the eponymous KASH domain and its interaction. The KASH domain is a C-terminal sequence of some 50–60 amino acid residues. It features a single membrane-spanning region followed by a short sequence of 40 residues or less that extends into the PNS. The KASH domain is both necessary and sufficient for targeting to the ONM. In C. elegans, the SUN-KASH assemble, the SUN domain, 1, 2, 3, 4, 5 (SPAG4), 5 (SPAG4L), and osteopontin. Of these, only two, SUN1 and SUN2, are widely expressed. Both SUN1 and SUN2 (as well as SUN3-5) are type II membrane proteins. The SUN1 and SUN2 N-terminal domains (~200–400 residues) are exposed to the nucleoplasm where they may interact with a variety of nuclear components, including members of the lamina family. The C-terminal region of SUN1 and SUN2 extends into the PNS. A membrane proximal sequence, which forms a triple helical coiled-coil (7), terminates in the globular SUN domain. It is now clear from studies in both mammals and C. elegans that SUN and KASH domains directly interact. In this way INM SUN domain proteins provide a unique function as transluminal tethers for ONM KASH proteins. The implication of these findings is that together, SUN and KASH domain proteins form a pair of links in a molecular chain spanning both nuclear membranes that physically couple nuclear components to the cytoskeleton. These SUN-KASH pairs are termed LINC complexes (for linker of the nucleoskeleton and cytoskeleton). Recent structural studies reveal that in mammalian SUN2, the SUN domain functions as a homo-trimer (7). KASH-domain binding involves extended interactions at the interface between two adjacent SUN domains. This association may be stabilized by the formation of an interchain disulfide bond between a cysteine within the KASH domain and an adjacent SUN domain cysteine. SUN2 (and in all likelihood, SUN1) trimerization is mediated by the membrane proximal luminal coiled-coil domain. This domain has a predicted length of 40–50 nm, sufficient to span the PNS and to bring the trimeric SUN domains close to the ONM where they can bind KASH sequences. The molecular modeling indicates that each SUN protein trimer has the capacity to bind three KASH domains. Accordingly, if individual KASH proteins are able to couple nuclear components to the cytoskeleton, as well as by the meiosis-specific proteins, Bqt-1, 2, 3, and 4. Through this chain of interactions spanning the NE, Kms1-associated dynein drives the clustering of KASH proteins, as well as the subsequent “horsetail”-like nuclear movements that are thought to facilitate homologous chromosome pairing. Budding yeast also utilizes LINC complexes to mediate bouquet formation. However, it is unusual in that the process is actin-rather than microtubule-mediated (8). Meiosis in C. elegans follows the S. pombe archetype where homolog pairing is facilitated by dynein-dependent bouquet formation. In the nematode, however, association of chromosomes with the NE is not mediated by telomeres. Instead, chromosome specific pairing centers (PCs) are used. ZYG-12, a KASH domain protein of the ONM and functional homolog of Kms1 functions as an adaptor for cytoplasmic dynein. An INM SUN domain protein, SUN-1/matefin (MTF-1), tethered ZYG-12 in the ONM and at the same time defines attachment sites for chromosomal PCs (9). This association between SUN-1/MTF-1 and PCs, is mediated by soluble chromosome- and PC-specific proteins (ZIM-1, -2, -3, and HIM-8). LINC complexes are also implicated in mammalian meiotic progression. Gene knockout studies in mice revealed that the INM SUN domain protein, SUN1, is essential for gametogenesis (10). Both males and females deficient in SUN1 are infertile. Infertility in males is clearly due to the arrest of primary spermatocytes in meiotic prophase 1, with the complete failure of telomeres to localize appropriately to the nuclear periphery. These studies demonstrate that, as with fusion yeast, telomere association with the NE is a prerequisite for bouquet formation and efficient homolog pairing. Telomere clustering always occurs at the pole of the nucleus that is closest to the centromere or microtubule organizing center (MTOC, reviewed in refs. 6 and 58). By
analogy with *S. pombe* and *C. elegans*, this is likely to be a dynein-mediated process requiring the function of a meiotic LINC complex that couples telomeres to the microtubule system. While SUN1 clearly represents the INM portion of such a LINC complex, the identity of its ONM KASH domain portion has until very recently remained uncertain.

KASH5: A New Dynein Adaptor

A candidate KASH component of a meiotic LINC complex, KASH5, was first revealed in a yeast two-hybrid screen of a mammalian testis library using the mouse cohesin protector protein, shugosin 2, as bait. Although this interaction was likely an artifact, characterization of KASH5 revealed localization to the NE of primary spermatocytes in a SUN1-dependent manner. Furthermore it was found to associate with p50GAP, a component of the dynein regulatory complex, dynactin. In complementary studies, we had searched for new proteins that displayed sequence homology with the Nesprin KASH domain. We were able to identify two additional KASH domain proteins, Nesprin-4 and lymphocyte restricted membrane protein (LRMP, also known as JAW1). Both of these proteins display SUN1/2- and KASH domain-dependent localization to the ONM. Furthermore it was found to associate with p150Glued, a component of the dynein regulatory complex, dynactin. In complementary studies, we had searched for new proteins that displayed sequence homology with the Nesprin KASH domain. We were able to identify two additional KASH domain proteins, Nesprin-4 and lymphocyte restricted membrane protein (LRMP, also known as JAW1). Both of these proteins display SUN1/2- and KASH domain-dependent localization to the ONM. In the case of Nesprin-4, we now know that its function as an ONM, as an epithelial NE adaptor for Kinesin-1. A second homology search using the complete LRMP sequence as a probe detected a zebrafish KASH protein, Futile Cycle (Fue). Fue is required for dynein-dependent nuclear migration in zebrafish zygotes. When aligned with mouse LRMP, Fue displays an N-terminal extension that contains its dynein-binding region. Yet a third homology search using the unique Fue sequence revealed mouse KASH5. Further in silico analysis of the complete KASH5 sequence of 578 amino acid residues highlighted a degenerate, but nevertheless recognizable C-terminal KASH domain, a central predicted coiled-coil and an N-terminal domain containing a calmodulin-like EF-hand sequence.

Consistent with the observations of Morimoto et al. (2012), we confirmed that in adult mice, KASH5 expression was restricted largely to the testis. However, RT-PCR also detected the presence of KASH5 transcripts in bone marrow derived cells. Although no cell lines could be found that expressed KASH5 at any level, when recombinant KASH5 was introduced into HeLa or HEK293T cells it localized to the ONM. This localization was dependent upon the integrity of its KASH domain as well as upon the presence of SUN1 or SUN2. Significantly, KASH5 was able to recruit cytoplasmic dynein and associated regulatory molecules (e.g., the dynactin...
complex and LIS1) to the NE. Recruitment depends on the KASH5 N-terminal domain containing the EF-hand motif. Related experiments, in cultured cells, revealed that KASH5 can self-associate through the central coiled-coil domain. Taken together, these findings indicate that KASH5 defines a new LINC complex species that couples the NE and associated nuclear structures to the microtubule system via cytoplasmic dynein. The fact that KASH5 can oligomerize also suggests that KASH5 LINC complexes could potentially form large arrays or clusters.

SUN1 is the predominant SUN domain protein expressed in spermatocytes. By conventional immunofluorescence microscopy it appears to be distributed across the spermatocyte nuclear surface as discrete foci. Each of these foci is coincident with a telomere attachment site. Furthermore, SUN1 and KASH5 precisely co-localize, consistent with the notion that these two molecules assemble to form a mosaic LINC complex. Such a suggestion is reinforced by the finding that KASH5 is lost from the spermatocyte NE in mice deficient in SUN1.

To better define the physiological role of KASH5 we derived mice in which both KASH5 alleles were non-functional. While KASH5-null mice are healthy with an apparently normal lifespan, both males and females are infertile. In the males no mature sperm cells are produced whatsoever. A more careful analysis reveals that spermatogenesis is arrested during meiotic prophase 1. Arrest was at pachytene and was associated with a failure to resolve double strand DNA breaks. Loss of maturing sperm coincided with extensive apoptosis (as measured by TUNEL staining) in the seminiferous tubules. If as we suspected that KASH5-containing LINC complexes are required for telomere clustering and efficient homolog pairing then prophase arrest should be occurring prior to synaptonemal complex formation. SCs contain two major structural features. Axial elements assemble as a strip along the entire length of each homolog. During the final stages of SC formation axial elements become linked by a series of transverse elements akin to the rungs of a ladder. By following the recruitment and assembly of the axial element protein SCP3 and the transverse element protein SCP1 it is possible to follow the progress of synopsis. This analysis was greatly facilitated by the use of structured illumination microscopy (SIM), a super-resolution technique that allowed us to resolve paired axial elements, which in synapsed chromosomes, are separated by a distance of only 100–150 nm.

Figure 3. Structured illumination microscopy of spermatocytes labeled with antibodies against KASH5 and SCP3. KASH5 is organized into ring or figure-eight-like structures.

Unanswered Questions

There are still a number of issues to be addressed concerning the function of meiotic LINC complexes in mammals. While it is clear that SUN1 defines NE attachment sites for telomeres the nature of the interaction and its regulation remain unknown. Whether the association between SUN1 and telomeres or shelterin complex components is direct or whether there might be other meiosis-specific
molecules involved that are similar in function to Bqt1–4 in S. pombe remains unknown. Both zebrafish Fue and C. elegans ZYG-12 have essential roles in pronuclear migration in early embryos. This activity is linked to the recruitment of dynein to the NE. This obviously raises the possibility that KASH5 might have a similar role following fertilization in mammals. Further studies using conditional mouse strains are being pursued to test this hypothesis as well as to explore the role of KASH5 in female germ cell development.

Disclosure of Potential Conflicts of Interest
No potential conflict of interest was disclosed.

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