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Review

SUN-domain and KASH-domain proteins during development, meiosis and disease

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Abstract. SUN-domain proteins interact directly with KASH-domain proteins to form protein complexes that connect the nucleus to every major cytoskeleton network. SUN-KASH protein complexes are also required for attaching centrosomes to the nuclear periphery and for alignment of homologous chromosomes, their pairing and recombination in meiosis. Other functions that require SUN-domain proteins include the regulation of apoptosis and maturation and survival of the germline. Laminopathic diseases affect the distribution of the SUN-KASH complexes, and mutations in KASH-domain proteins can cause Emery Dreifuss muscular dystrophy and recessive cerebellar ataxia. This review describes our current knowledge of the role of SUN-KASH domain protein complexes during development, meiosis and disease.

Keywords. Centrosome, cytoskeleton, Emery Dreifuss muscular dystrophy, homologous pairing, meiosis, nuclear positioning.

Introduction

In all eukaryotic cells the nuclear envelope (NE) separates the nucleus from the cytoplasm. It is composed of outer and inner nuclear membranes (ONM and INM, respectively). The two membranes fuse at nuclear pore complexes (NPCs). In all metazoans, the INM is anchored to a structural network of lamin intermediate filaments (IFs). The nuclear lamina is composed of lamin filaments and lamin-associated proteins, including many integral proteins of the INM (reviewed in [1, 2]). Nuclear architecture, cell cycle progression, DNA replication and RNA transcription and pre-mRNA splicing all depend on lamins [3, 4]. Mutations in lamins or in their associated proteins cause approximately 20 clinically different diseases, collectively termed laminopathies, ranging from muscular dystrophies to early aging diseases. These diseases affect many types of cells including adipocytes, muscle, skin, bone, blood and nerve cells [5–7].

Lamins are proposed to anchor multi-protein complexes in which integral proteins of the INM and ONM interact across the lumen between the membranes, 'bridging' the NE and mechanically coupling the nucleoskeleton and cytoskeleton. The key players in the bridging process are members of the SUN-domain and the KASH-domain protein families [8, 9] (Fig. 1). Recently, it became evident that SUN-domain proteins are much more than just linkers between the nucleus and cytoplasmic filamentous networks. Our

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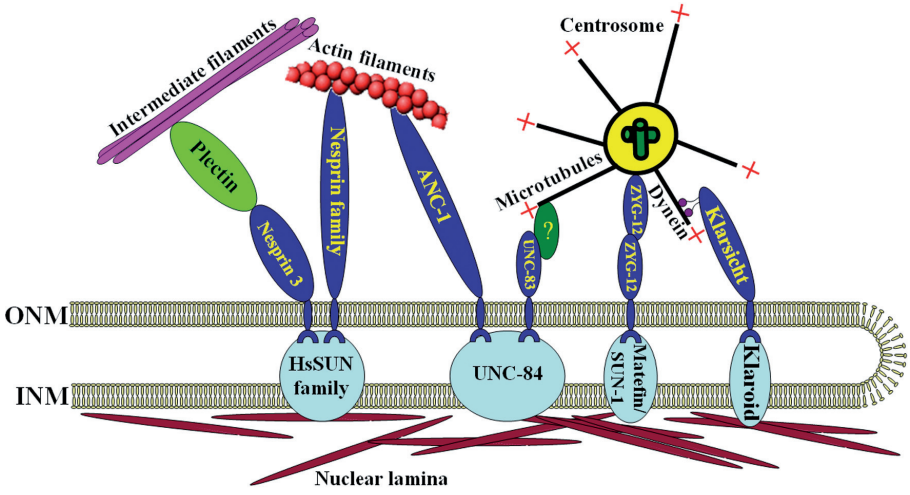

Figure 1. Mechanical bridging across the nuclear envelope by SUN-KASH domain proteins. Schematic depiction (not to scale) of the interactions between SUN-domain proteins (light blue) and KASH-domain proteins (dark blue) at the inner and outer nuclear membranes (INM and ONM, respectively) of the NE, and their interactions with specific elements of the cytoskeleton. The protein that links UNC-83 to the microtubules is currently unknown (?).

review will focus on those various newly emerging and exciting functions of SUN-domain proteins and their binding partners.

Min Han and his colleagues coined the name "SUN-domain" (Sad1 and UNC-84 homology domain), when they cloned the *Caenorhabditis elegans* (*C. elegans*) *unc-84* gene and discovered that the UNC-84 protein contains a motif of ~120 residues in its carboxyl part that shares a significant homology with a region in the *Schizosaccharomyces pombe* (*S. pombe*) Sad1 protein, as well as with several, then uncharacterized, mammalian proteins [10]. Very quickly it became evident that SUN-domain proteins are conserved in most or all eukaryotes and that the number of SUN-domain proteins has increased in evolution. For example, the *S. pombe* and *Dictyostelium discoideum* genomes each contain a single SUN-domain gene, named *sad1* and *sun-1*, respectively [11, 12]. *Saccharomyces cerevisiae* (*S. cerevisiae*), *C. elegans* and *Drosophila melanogaster* (*D. melanogaster*) each have two SUN-domain genes: *mps3* and *slp1*; *unc-84* and *mtf-1/sun-1*; *klaroid* and *CG6589,* respectively [10, 13–15], and humans have at least five SUN-domain genes: *SUN1*, *SUN2*, *SUN3, SUN4* (*SPAG4*) and *SUN5* (*SPAG4Like)* [8, 9, 16, 17]. In addition to the carboxyl SUN-domain, these proteins share some structural features; they contain at least one putative transmembrane domain and a less conserved coiled-coil domain. Most of them are localized to the INM [8].

Min Han and colleagues also suggested the name KASH-domain (Klarsicht/ANC-1/Syne-1 homology-domain) [18]. Members of this family contain a carboxy terminal transmembrane domain included in the ~60-residue KASH-domain. The KASH-domain proteins also constitute a fast growing family and their number has increased in evolution [9]. The KASH-domain is necessary and sufficient for NE localization [19, 20]. In addition to KASH-domain proteins localizing at the ONM, isoforms of the KASH-domain proteins Nesprin (known also as Syne/Myne/Enaptin and NUANCE) were detected in the nucleus, where they are probably associated with the INM [19, 21]. In these cases, it was previously hypothesized that their SUN-domain partners are present on the ONM [8, 22].

Lee et al. [22] were first to suggest the bridging model, in which SUN-domain proteins that span the INM bind KASH-domain proteins that span the ONM allowing a connection between the nuclear lamina and cytoplasmic components. The cloning of the *C. elegans* KASH-domain genes *unc-83* and *anc-1*, which depend on the SUN-domain protein UNC-84 for their localization, provided experimental evidence for the bridging model and suggested that these complexes are involved in linking the nuclear lamina to actin and tubulin networks [23, 24]. Further studies have shown that the SUN-KASH protein complexes are required for anchoring the centrosome to the nuclear periphery in early *C. elegans* embryo [25] and for the association between cytoplasmic IFs and the nuclear lamina [26].

SUN-KASH proteins are required for nuclear migration

Many cellular and developmental events, including fertilization, cell migration, cell division and more, depend on proper nuclear location. Two distinct but related processes, nuclear migration and anchorage, are required for proper positioning of nuclei (reviewed in [24, 27]. These processes are controlled by a combination of forces coming from microtubule and actin-based networks (Fig. 1). Interestingly, the *C.*

elegans UNC-84 protein is involved in both processes [10]. After the 24-cell stage, UNC-84 localizes to the NE in all *C. elegans* somatic cells [22]. This NE localization depends on nuclear lamin, which probably interacts with the UNC-84 N-terminus [22]. Null *unc-84* mutations lead to an uncoordinated (*unc*) phenotype because failed nuclear migrations lead to the death of P-cells, which normally migrate from the lateral sides of the newly hatched larva to form a single row in the ventral cord [28]. The second nuclear migration event defective in *unc-84* mutants occurs during the morphogenesis stage of embryogenesis, when the hyp7 precursor cells go through a series of elongation and nuclear migration events, including nuclei movement past the dorsal midline to the opposing lateral side within the cytoplasm [29, 30]. In *unc-84*-null mutants, the nuclei move slowly and do not migrate beyond the dorsal midline and float freely within the hyp7 syncytium [10]. Some *unc-84* animals also display defective nuclear migration in cells of the intestinal primordium [23]. UNC-84 functions are probably dispensable in other cell types.

UNC-83 is an ONM protein containing a conserved C-terminal KASH-domain [20]. Mutations in *unc-83* also disrupt nuclear migration in P cells, hyp7 precursors and the intestinal primordium, except that the nuclei do not float freely within the cytoplasm of the hyp7 syncytium [23]. Unlike UNC-84, UNC-83 only localizes to specific nuclei, many of which are migratory at specific stages of development. UNC-84 probably depends on UNC-83 for regulating nuclear migration, since loss of UNC-84 affects only a small number of migrating nuclei that are UNC-83-positive in the developing embryo and larvae, although UNC-84 is expressed in most cells [22, 23].

Mutations in the KASH-domain of UNC-83 or in the SUN-domain of UNC-84 result in a failure of UNC-83 to localize to the NE. In addition, UNC-83 interacts with the SUN-domain of UNC-84 *in-vitro*, suggesting that these two proteins function together during nuclear migration and supporting the model that SUN- and KASH-domain proteins bridge the NE, thereby connecting the nuclear lamina to cytoskeletal components [22]. In this model UNC-84 localizes to the INM with its N-terminus associated with the nuclear lamina and its C-terminal SUN-domain facing the lumen of the nuclear envelope. UNC-84 helps recruiting UNC-83 to the ONM through direct interactions in the lumen. The cytoplasmic domain of UNC-83 probably binds the tubulin network through specific motors, which would allow nuclear migration.

The *Drosophila* KASH-domain protein Klarsicht (Klar) is a 250 kDa protein with a KASH-domain required for nuclear localization in photoreceptor cells. In *klar* mutants lacking a functional KASH-domain, the apical nuclei in the developing compound eye of *Drosophila* fail to migrate. Failure of this migration affects cell shape and overall compound eye morphology. Most nuclei remain at the basal side, which results in oddly shaped photoreceptors [31, 32]. Overexpression of the Klar KASH-domain in photoreceptor cells does not result in a mutant phenotype [31], suggesting that it does not compete with the endogenous protein for a limited number of binding sites at the NE. Klaroid (Koi) is a *Drosophila* SUN-domain protein localized to the nuclear periphery. This localization requires the *Drosophila* lamin C. In turn, Koi is required for Klar nuclear periphery localization [15]. Klar probably facilitates nuclear migration by linking the nucleus to the cytoskeleton, likely thought to coordinate opposing forces from dynein and kinesins on the microtubules towards the centrosome [33].

Taken together, the current data show a role for SUN-KASH domain proteins in nuclear migration in *C. elegans* and *Drosophila.* It remains to be seen if this role of SUN-KASH domain proteins is conserved in higher eukaryotes [27, 34].

SUN-KASH proteins anchor the nucleus

Mutations in *unc-84* also cause nuclear anchorage defective (*anc*) phenotype, in which nuclei in syncytial cells float freely within the cytoplasm and multiple nuclei group together [10, 35]. The SUN-domain is required for this function, since the *anc* phenotype is observed only when the SUN-domain of UNC-84 or sequences in its vicinity are mutated [10]. The switch between nuclear anchorage and the nuclear migration function of UNC-84 must be tightly regulated. Studies on different binding properties of UNC-83 and ANC-1 to UNC-84 and/or the post-translational modifications of UNC-84 may help understanding how this switch is regulated.

Mutations in the *C. elegans anc-1* gene cause nuclear anchorage defects but not nuclear migration phenotypes. ANC-1 is a giant, 8546-residue, protein containing a KASH-domain. It is mostly composed of coiled regions, including six repeats of 903 residues that are nearly 100% identical to each other [24]. ANC-1 NE localization depends on the SUN-domain of UNC-84 and on an intact KASH-domain [24]. Overexpression of the KASH-domain of ANC-1 causes phenotypes similar to *anc-1* mutations, suggesting that the isolated KASH-domain occupies the available docking sites of ANC-1 at the NE.

ANC-1 belongs to a family of KASH-domain proteins also conserved in *Drosophila* and vertebrates. In

addition to the KASH-domain, *Drosophila* muscle-specific protein 300 (Msp-300) and mammalian Nesprin-1 and Nesprin-2 share a large central domain of multiple spectrin repeats that could function analogously to the long coiled domains of ANC-1, probably by enabling the proteins to stretch over a long distance [36]. The N-terminus of ANC-1 is also similar to that of Msp-300 and the Nesprin proteins contain two approximately 100 residue-long regions of homology to the calponin domains of human alpha-actinin, suggesting that the amino terminal domain of these KASH-domain proteins interacts with the actin cytoskeleton. It is possible that the length of these KASH-domain proteins, which is estimated to be between 0.5–1 microns, would be sufficient for tethering the nucleus to the actin cytoskeleton. However, there are currently no data available on the stiffness or flexibility of the extended rod portion.

The role of KASH-domain proteins in nuclear anchoring is conserved in mice. During muscle fiber formation, 3–8 synaptic nuclei are clustered at the neuromuscular junction, while other nuclei distribute evenly in the syncytial muscle fibers. Nesprin-1 and Nesprin-2 are expressed in the skeletal muscle [37, 38]. The clustering of the synaptic nuclei was disrupted in mice when Nesprin-1 was replaced with Nesprin-1 lacking its KASH-domain. In addition, in these mice, the non-synaptic nuclei of the skeletal muscle were clustered instead of being distributed evenly [39]. The disrupted clustering of synaptic nuclei in the Nesprin-1-knockout mice significantly affected the innervation sites and caused longer motor nerve branches [39]. In contrast, mice lacking Nesprin-2 did not show the muscle fiber nuclear clustering phenotype, making Nesprin-2 dispensable for the myonuclear positioning process. Ectopic expression of the KASH-domain of Nesprin-1 in transgenic mice caused disruption of synaptic nuclei clustering, similar to the ectopic expression of the KASH-domain of ANC-1 in *C. elegans*, but had no effect on the even spacing of non-synaptic nuclei [40]. Similar results were observed following ectopic expression of the Nesprin-2 KASH-domain in transgenic mice [39], suggesting that the KASH-domain of Nesprin-2 has the ability to bind targets of the KASH-domain of Nesprin-1.

The role of Nesprin-2 was also analyzed in mice in which the endogenous copy of *Nesprin-2* was replaced with *Nesprin-2* lacking the region encoding the amino-terminal actin-binding domain. Nuclei of primary dermal fibroblasts and keratinocytes showed abnormal shape, similar to nuclei expressing mutant lamins A/C [41]. Emerin, an integral protein of INM that interacts with both lamin and Nesprin-2 [42], formed aggregates. Surprisingly, there were no apparent abnormalities in skin morphology or histology *in vivo* [41].

Nesprin-1 and Nesprin-2 have other overlapping functions, since mice lacking both proteins die shortly after birth due to inability to breathe, while each separate knockout has a very mild effect. The mechanism behind this respiratory failure is still unknown [39].

The *Drosophila* Msp-300 is expressed in somatic, visceral and heart embryonic muscle and in germline, where it interacts with the actin network. Mutations in the *Drosophila msp-300* gene cause larval lethality and muscle morphology defects [43]. Msp-300 is also expressed in the eye, where it is not required for nuclear positioning [44]. During late stages of *Drosophila* oogenesis, the cytoplasm of nurse cells in the egg chamber is rapidly transferred to oocytes. The nurse cell nuclei are anchored by a mechanism that prevents them from moving to the oocyte, which involves the actin network. The role of Msp-300 in this process is controversial. In one report, Msp-300 was required to prevent this movement of nurse cell nuclei into the ring canals, since in *msp-300* mutants, nurse cell nuclei were found in oocytes or blocking the ring canals. In addition, the normally anchored oocyte nucleus floats freely [45]. Two recent reports challenge these roles of Msp-300 in nuclear anchoring in oogenesis and show that deletion of the Msp-300 KASH-domain or a complete deletion of the *msp-300* gene did not cause nuclear anchorage defects in *Drosophila* nurse cells or in the oocyte, suggesting nuclear anchoring phenotypes in *Drosophila* oogenesis are caused by a different, probably closely linked, gene [44, 46].

In summary, the current data suggest a role of SUN-KASH domain complexes in nuclear anchoring in *C. elegans* and in vertebrates. The role of these complexes in nuclear anchoring in *Drosophila* is still in debate.

SUN-KASH proteins anchor the centrosome to the nucleus

In most interphase cells, the centrosome is associated with the nucleus. Disengagement of the centrosome from the nucleus can sometimes lead to a failure of astral microtubules to capture mitotic chromosomes, therefore producing defects in the segregation of chromosomes. Mutations in the *C. elegans zyg-12* gene cause detachment of the centrosome from the nuclear periphery [25]. ZYG-12 is a KASH-domain protein present both at the centrosome and in the ONM. The *zyg-12* transcript is alternatively spliced to produce two isoforms with a KASH-domain and one isoform without it. The common amino-terminal region of

ZYG-12 is homologous to the Hook family of proteins, which probably link membrane compartments to the microtubule cytoskeleton [25]. Localization of ZYG-12 to the centrosome requires microtubules and its localization to the NE requires the SUN-domain protein matefin/SUN-1. It was suggested that ZYG-12 directly mediates the attachment of the centrosome to the nucleus via the ability of the different isoforms to form dimers. ZYG-12 also helps localizing dynein to the NE. According to the suggested model [25], proximity is established between the centrosome and nucleus via dynein-mediated translocation of the nucleus toward the minus ends of astral microtubules emanating from the centrosome. Once proximity has been established, attachment is initiated and maintained by ZYG-12 in a dynein-independent manner. Downregulation of *mtf-1/sun-1* causes centrosome detachment and displacement of ZYG-12 from the ONM in the very early embryo [25]. Although matefin/SUN-1 interacts with ZYG-12 in other cells, at later stages of development and in the gonad, matefin/SUN-1 is not required for centrosome attachment to the nucleus during these stages (A.F. and Y.G. unpublished observations and [47].

The role of SUN-KASH domain protein complexes in centrosome attachment in mammals is still unknown. In human dermal fibroblasts, emerin is required for linking centrosomes to the nucleus [48]. Emerin is an integral protein residing principally at the INM [42], where it interacts with lamins and forms large protein complexes [49]. Emerin can also interact with Nesprin isoforms, as was shown for Nesprin-1α [21] and Nesprin-2 [38], and its localization at the INM depends on both Nesprin-1α and Nesprin-2β [50]. However, a significant fraction of emerin is also present at the ONM, where it interacts with β-tubulin [48]. Taken together, these data imply that emerin interacts with β-tubulin to anchor the centrosome at the ONM in human fibroblasts, and SUN- and/or KASH-domain proteins may assist this interaction.

SUN-domain proteins in apoptosis

Surprisingly, matefin/SUN-1 is involved in apoptosis. In *C. elegans* the anti-apoptotic protein CED-9 is localized at the mitochondria, where it binds the pro-apoptotic protein CED-4. Induction of apoptosis begins when the pro-apoptotic BH3-domain protein EGL-1 is expressed and binds CED-9. The binding of EGL-1 to CED-9 releases CED-4 from CED-9 and causes the activation of the caspase CED-3 (reviewed in [51]). Upon its release from CED-9, CED-4 rapidly translocates to the NE in a CED-3-independent manner [52].

CED-4 binds directly to matefin/SUN-1 *in vitro* and matefin/SUN-1 is required for CED-4 NE localization and maintenance, suggesting that matefin/SUN-1 is the CED-4 receptor at the NE [53]. The significant reduction in the number of apoptotic cells in embryos down regulated for matefin/SUN-1 indicates that the binding between CED-4 and matefin/SUN-1 is required for the execution of apoptosis. It also indicates that SUN-domain proteins can function as receptors that link cytoplasmic components to the NE in a KASH-domain independent manner, thus connecting cytoplasmic processes to the nucleus.

It is worth noting that although the core apoptotic pathway is conserved in vertebrates [54], there is currently no experimental evidence that SUN-domain proteins are also involved in vertebrate apoptosis.

SUN-KASH domain proteins in meiosis

Haploidization of the chromosome complement is a prerequisite of gametogenesis in all sexually reproducing eukaryotic organisms. Halving the chromosome number is accomplished during the specialized nuclear divisions of meiosis by partitioning homologous chromosomes (homologues) during the first meiotic segregation step. The reductional division of meiosis I is directly followed by a second segregation step, disjoining sister chromatids, without a preceding second DNA replication phase.

To faithfully separate homologues, the chromosomes have to find their respective partner and engage in a stable physical association before being pulled into opposite directions of the cell by the meiotic spindle. Homologous pairing is a highly dynamic process that relies on the pronounced movement of the chromatin during early meiotic prophase I. Recent data underline a conserved function for SUN-domain carrying proteins in homologue disjunction by mediating telomere attachment to the NE and chromosome dynamics in early meiosis of eukaryotic organisms. We would like to discuss the contribution of SUN-domain proteins to meiotic chromosome movement, as well as the consequences that an impairment of chromosome movement has in different model organisms (covering yeasts, *C. elegans* and mammals). SUN-domain proteins from the plant kingdom still await characterization.

Chromosome behaviour during meiotic prophase I

During meiotic prophase I, maternal and paternal homologous chromosomes undergo morphological changes and spatial rearrangements within the nucleus, in preparation for their faithful partitioning during the first meiotic division. The correct alignment of homologues on the metaphase I spindle followed by their faithful disjunction relies on their mutual recognition and the formation of a stable association via reciprocal recombination between pairs of homologues (bivalents). Chromosome pairing can be envisioned as a multi-step process during which chromosomes are first aligned at a certain distance before they are paired in close proximity and finally stably synapsed along their entire length in most organisms [55]. Synapsis is defined as the establishment of a proteinaceous structure, the ladder-like synaptonemal complex composed of lateral and central elements, between homologous chromosomes. In meiosis, one or both chromosome ends attach to the NE and remain anchored from leptotene to late pachytene [56]. Dispersed attached telomeres are moved transiently and are concentrated in a limited volume of the nucleus at the leptotene/zygotene transition prior to homologous pairing. The polarized configuration of telomeres, also called the chromosomal bouquet, is a conserved phenomenon, but the degree of polarization varies between model organisms. Concomitant with the movement of telomeres, chromosomes are rearranged. The timing of this clustering coincides with chromosome pairing, synapsis initiation and processing of recombination intermediates (for review, see [57, 58]). Telomere clustering is followed by the dispersion of telomeres, and pronounced telomere-led chromosome movements are observed at later stages of meiotic prophase [57, 59, 60].

Attachment of chromosome ends to SUN-domain proteins

Before telomeres are moved along the nucleoplasmic surface of the INM, chromosome ends have to stably attach to the NE. SUN-domain proteins might therefore act as putative adaptors for chromosome ends to the NE via their nucleoplasmic N-terminus. Indeed, recent data clearly establish a role of SUN-domain proteins in the localization of chromosome ends to the nuclear periphery.

Saccharomyces cerevisiae

The absence of the *S. cerevisiae* meiosis-specific telomere binding protein Ndj1/Tam1 leads to random localization of chromosome ends within the nucleus instead of perinuclear localization [61]. Importantly, Ndj1 displays robust colocalization with Mps3, a *S. cerevisiae* SUN-domain protein, at telomeres in spread meiotic nuclei, and both proteins mutually stabilize their telomere association. Indeed, Mps3 and Ndj1 interact *in vivo* and the interaction domain has been mapped by a yeast-two-hybrid analysis to its N-terminal residues 2–64. Consistently, like *ndj1Δ*, $mps3^{\Delta 2-64}$ mutants are defective in telomere attachment and peripheral chromosome distribution [59, 62]. While the chromosomes are frequently peripheral in the wildtype nucleus, in $mps3^{\Delta 2-64}$ cells chromosomes adopt a more even nuclear distribution [59]. Taken together, the data suggest that Mps3 stably interacts with telomeres through binding to the meiotic telomere protein Ndj1. The *S. cerevisiae* SUN-domain protein Mps3 thereby promotes telomere clustering and contributes to homologous pairing and synapsis, resulting in a faithful haploidization of the chromosome complement [61, 62]. Recent findings demonstrate that Ndj1 and Mps3 interact with Csm4, another meiotically induced tail-anchored NE protein that is implicated in meiotic chromosome segregation [59, 63]. Although Ndj1 and Mps3 are required for the localization of Csm4 at meiotic telomeres in surface-spread nuclei and all three proteins co-immunoprecipitate in a complex *in vivo*, Csm4 is not required for the telomeric localization of either Ndj1 or Mps3, and consistently is also not required for the attachment of chromosome ends to the NE. This argues for an additional function of Csm4 within the complex at the NE [59].

Schizosaccharomyces pombe

In *S. pombe* both the SUN-domain protein Sad1 and its KASH-domain partner Kms1 are integral components of the spindle pole body which is embedded in the NE, and are, therefore, essential for viability [11, 64–66]. Sad1 and Kms1 colocalize at the spindle pole, and Sad1 can only be detected around the NE very transiently in wildtype cells. It is also localized around the NE under conditions that disrupt the nucleo/cytoplasmic linkage, as in a Kms1 mutant or upon overexpression of Sad1 (for review see [67]). This could be interpreted to mean that in the wildtype the concentration of telomeres in the bouquet could represent the final parking position following a very rapid movement. The meiosis-specific proteins Bqt1 and Bqt2 are found in a protein complex that establishes the meiosis-specific connection of the chromosome ends to Sad1 [68, 69]. Through binding to Bqt1 and Bqt2, Sad1 is able to form a complex with Rap1 at the telomeres. The N-terminus of Sad1 provides the interaction surface, consistent with the

proposed SUN-KASH topology. Interference with Bqt1 or Bqt2 function abrogates telomere movement into the bouquet (for review, see [70]). The phenotypic readout of depleting telomere components such as Taz1 or Rap1 suggests a role for the bouquet in both pairing and recombination [71–73]. Functional Kms1 supports intragenic recombination and inhibits ectopic recombination [65]. The results of depleting Bqt2 suggest that the bouquet also inhibits ectopic recombination, besides its requirement for intragenic recombination [74].

Caenorhabditis elegans

The C. *elegans* chromosomes contain a pairing center (PC) proximally to one telomere of each chromosome which is required for the stabilization of synapsis-independent homologous associations as well as for synapsis initiation of the individual chromosome pair [75]. It is this specific chromosome end that attaches to the NE upon entry into meiosis. The four PC proteins have zinc finger motifs and bind between one and two PCs of individual chromosomes.

In leptotene/zygotene chromosome ends, marked by PC-binding proteins (such as HIM-8 and ZIM-1-3), colocalize with aggregates of the SUN-domain protein matefin/SUN-1 (A.P. and V.J., unpublished). Matefin/SUN-1, however, is most likely not the primary anchor of chromosome ends to the NE, since the X-chromosomal PC-end still remains positioned at the nuclear periphery in its absence (A.P. and V.J., unpublished). How telomeres are tethered to the NE in *C. elegans* remains elusive but PC-binding proteins seem to play an important role in this process. Not only are the majority of PC-binding proteins cytologically detectable as soon as chromosome ends are attached to the NE, but more importantly, chromosome ends appear randomly localized in the nuclear volume in their absence [76]. Apart from the colocalization observed during the time window of chromosome pairing, no direct interaction between matefin/SUN-1 or its N-terminus and PC-binding proteins has been shown to date. Therefore, it seems plausible that additional and probably meiosis-specific proteins, including telomere-binding proteins, are involved in the establishment of a link between chromosome ends and matefin/SUN-1 at the NE. The colocalization of PC-binding proteins with matefin/SUN-1 might reflect the stable attachment of one chromosome end to the nuclear periphery that is required during a stage of extensive chromosome/telomere movement.

Mammals

In mammals, Sun1 and Sun2 have been implicated in meiotic chromosome segregation. Both proteins are ubiquitously expressed, continuously localized over the surface of the NE in somatic cells and are concentrated in distinct foci at the NE in meiotic prophase I. Sun1 forms aggregates that associate with telomeres from leptotene until diplotene [77]. In mammalian meiosis, telomeres attach to the NE by telomeric repeats through conical thickening of chromosomal ends detectable as an electron-dense plate by electron microscopy [78]. Sun2 has been specifically localized to these telomere attachment sites. It mostly co-localizes with thin filaments that span the nuclear membrane and connect to cytoplasmic fibrillar structures. This localization appears to be independent of axial elements and lamin C2, a splice variant of lamin A specifically found at chromosomal attachment sites [79].

Sun1 knockout mice are zygotically viable but both females and males are sterile. Both spermatids and spermatozoa are absent due to meiotic arrest and apoptosis. Most importantly, telomeres loose their NE localization and are detected in the interior of the nucleus in the majority of cells that display morphological characteristics of zygotene. In addition, telomere clustering is disturbed and synapsis is partial, although it still takes place between homologous chromosomes [77]. It is not yet known whether the interaction between Sun1 and the telomere is direct. SUN-domain proteins are not very conserved at their N-terminus, suggesting that different ways of building up the link between the chromosome and the SUN-domain protein might have evolved. On the other hand, the N-terminal zinc finger motif could potentially interact with chromatin [80]. The lack of a somatic phenotype for $Sun1^{-/-}$ could potentially be due to overlapping functions with Sun2. Thus, data on a Sun2 knockout and a Sun1-Sun2 double knockout are eagerly awaited to address whether these proteins act redundantly in the germline.

In general, the meiotic situation might differ from mitosis where alternative sub-domains of SUN-domain proteins and specific interacting components such as chromatin factors seem to be involved in localizing chromosome ends to the nuclear periphery [12, 81, 82]. The additional expression of telomere-binding proteins in meiosis and the assembly of a meiosis-specific telomeric protein complex might promote stable attachment of chromosome ends to the nuclear periphery, thereby generating an adaptor for active chromosome motility. Despite the strong conservation of the SUN-domain bearing key players that build a bridge from the nucleus to cytoplasmic forces, the components that connect SUN-domain proteins to meiotic telomeres seem to be much less conserved.

Movement/dynamics of chromosomes via a SUN-KASH protein bridge

During meiotic prophase I, chromatin displays highly dynamic movements and numerous studies demonstrate that the observed chromosome movement is an active process. What is known about the mechanism underlying chromosome motility and what are the phenotypic consequences of its absence?

As discussed above, SUN-domain proteins are crucial for the attachment of telomeres to the NE. The interaction of SUN-domain proteins with their KASH-domain carrying partners at the ONM establishes a potential connection of chromosome ends to cytoplasmic force-generating structures such as actin or microtubules. Indeed, there is compelling evidence that cytoplasmic-driving forces might promote chromosome motility across eukaryotes, indicating a conserved mechanism for meiotic telomere movement. SUN-domain proteins might not only play a role in the recruitment of telomeres to the NE, but also in their movement, thereby contributing to the organization of chromatin architecture and to homologue sorting during meiosis.

Saccharomyces cerevisiae

Visualizing yeast telomere behaviour by live imaging of GFP-tagged versions of the telomere-binding protein Rap1 or the telomere-associated protein Mps3, as well as by labelling specific yeast telomeres with the lacO/lacI-GFP system demonstrates pronounced telomere movement throughout meiotic prophase from leptotene to pachytene [59–61]. The motility of prophase chromosomes has been independently confirmed by time-lapse analysis of the axis protein Rec8-GFP and the synaptonemal complex central component Zip1-GFP, and it has been demonstrated that the chromosome movements are led by the respective telomeres. Attachment of telomeres to the NE is a prerequisite for chromosome motility in *S. cerevisiae*. The absence of Ndj1 or truncated $mps3^{\Delta 2-64}$ causes dramatic reduction in the movements of pachytene chromosomes [59, 60, 83]. Stable attachment of chromosome ends to the nuclear periphery, telomere clustering as well as the motion of pachytene yeast chromosomes seem to be promoted by actin filaments in *S. cerevisiae*, since the actin-depolymerizing drug latrunculin B (LatB) inhibits the formation of telomere clusters at leptotene and reduces the chromosome movements at pachytene to background levels [60, 83, 84]. Interestingly and in contrast to mammals, plants or fission yeast, chromosome movement is insensitive to microtubule (MT) drugs. Inhibition of microtubule polymerization only moderately influences telomere clustering in the leptotene/zygotene transition and does not detectably reduce pachytene motion [84]. The same is true for the deletion of the cytoplasmic dynein motor protein Dhc1 [60].

Importantly, pachytene movement of chromosomes is accompanied by local deformations of the nucleus. Nuclear shape changes are still observed when telomeres detach from the NE but are sensitive to the actin antagonist LatB, which is consistent with the notion that cytoplasmic actin cables that are observed in close proximity to the nucleus interact with the outside of the NE, where they exert force powering telomere movement [59, 60, 83, 84]. It has been suggested for yeast telomeres that they are passively attached at a fixed position along the actin cable, following the movements of the cables in the cytoplasm which results in concerted and individual movement of chromosomes [60].

It is not clear whether Mps3 establishes the connection to the actin cables' interaction with a KASH-domain carrying partner. Mps2, which interacts with the SUN-domain of Mps3 [85], could be considered as a putative KASH-domain partner contributing to the bridge across the NE. However, the involvement of Mps2 in meiotic chromosome movement has not yet been addressed and no *mps3* mutant has been isolated which retains telomere attachment in meiosis but displays reduced chromosome motion. It is likely that the NE protein Csm4, which is associated with chromosome ends via Mps3 and Ndj1, establishes the connection to the machinery that provides the force for chromosome movement, as telomere movement is almost abrogated in *csm4Δ* mutants and local shape changes of the nucleus are no longer documented [59, 60].

Severe reduction of prophase chromosome movement, which is observed when chromosome ends stay unattached to the NE, causes a delayed and slightly reduced homologue pairing, and leads to defects in recombination [61, 62, 86, 87].

Abrogation of movement in early meiosis by the addition of LatB right after the formation of many double strand breaks (DSBs) resulted in delayed DSB processing and repair, as well as reduced crossover formation, suggesting that chromosome movement is required for recombination [60]. Reduction of pachytene chromosome movements in the *csm4Δ* background caused increased associations of telomeres independent of recombination, suggesting that prophase movements disrupt associations that are not stabilized by recombination intermediates [59, 60]. Additionally, elimination of Csm4 function leads to an increase in cross-over frequencies, loss of cross-over interference, and a delay in cross-over maturation [88, 89]. Chromosome movement is required at the very early phase in meiotic recombination when it is

decided which recombination intermediates will mature into cross-overs [88]. The removal of ectopic, non-specific chromosomal interactions and entanglements by chromosome movement ensures homolog juxtaposition, a prerequisite for cross-over designation. Delays in this step may account for subsequent recombination defects. On the other hand, it was proposed that chromosome movement actively promotes later steps during recombination, such as second-end capture and resolution of double-Holliday junction by affecting chromatin structure [89], reviewed in [90].

Schizosaccharomyces pombe

Meiotic prophase I displays the unique feature of horsetail movement. It manifests itself through back and forth oscillation of the nucleus with the spindle pole at the leading edge of the nucleus. The nucleus elongates and chromosomes cluster opposite the spindle pole body [91, 92]. *In vivo* imaging of eight chromosomal loci along chromosomes in recombination wildtype or mutant backgrounds led to the following model: the bouquet clustering first bundles the chromosomes by restricting them in a limited space allowing their alignment. Nuclear oscillation then facilitates recombination, which requires close association of chromosomes. As a consequence, allelic recombination is reduced in mutants affecting both bouquet formation and horsetail movement. Interference with the microtubule motor Dhc1, a yeast-two-hybrid interactor of Kms1, caused a reduced frequency of chromosome pairing and disruption of horsetail movement [74, 93]. While oscillatory movement of the nucleus is driven by astral microtubules and dynein motors, clustering of telomeres does not depend on the dynein motor Dhc1 [74, 94, 95]. Interestingly, ectopic recombination is elevated only in the telomere clustering mutant background, leading to aberrant chromosomal fusions and chromosome missegregation. These data suggest that although telomere clustering and horsetail movement contribute to chromosomal pairing, the two processes of movement contribute in genetically separable ways [74]. The available data strongly support a role for SUN-KASH-mediated movement in the process of telomere clustering. The involvement of this module in horsetail movement is harder to assess, since those components are vital for spindle pole body function.

Caenorhabditis elegans

Little is known about chromosome movement in the prophase of *C. elegans* meiosis. In leptotene/zygotene, concomitant with the establishment of first homologous chromosome contacts, meiotic chromatin adopts a polarized configuration. These nuclei are also referred to as transition zone nuclei. Importantly, chromosomes do not cluster at the centrosome-facing pole.

In the transition zone, matefin/SUN-1-GFP forms highly dynamic aggregates at the sites where PC-containing chromosome ends are tethered to the NE, suggesting that the movement of matefin/SUN-1-GFP aggregates mirrors the movement of chromosome ends at the nuclear surface (A. Baudrimont, A.P. and V.J., unpublished). This analysis is comparable to the examination of the mobility of the SUN-domain protein Mps3-GFP in budding yeast, which also visualized the dynamics of telomeres in meiotic prophase [59]. The movement of the matefin/SUN-1-GFP aggregates is restricted to a sub-volume of the nucleus, which is consistent with the chromatin displaying a half-moon shape in fixed preparations since the nucleolus occupies the other half. Within the nuclear sub-volume, smaller matefin/SUN-1-GFP aggregates coalesce into bigger aggregates, which potentially resolve into smaller ones, suggesting that chromosome ends dynamically encounter each other and re-disperse.

C. elegans matefin/SUN-1 was shown to retain the KASH-domain protein ZYG-12 at the NE via a functional SUN-domain [25, 47]. These data argue that a SUN-1/ZYG-12 bridge is established across the NE in *C. elegans.* At the cytoplasmic side, ZYG-12 is required for dynein localization to the NE and interacts with the dynein subunit DLI-1 in a yeast-two-hybrid assay [25]. Interestingly, in the SUN-domain-defective mutant *jf18*, SUN-1(G311V)-GFP no longer forms aggregates but rather displays static foci colocalizing with PC-binding proteins (A. Baudrimont, A.F., A.P., Y.G. and V.J., unpublished), thus suggesting that telomere movement in the transition zone requires a functional SUN-domain. This result agrees with the idea that chromosome ends are moved by a cytoplasmic force that is transmitted to the nuclear interior via a ZYG-12/matefin/SUN-1- bridge. It will, therefore, be interesting to see whether actin and/or microtubule drugs have an effect on chromosome movement in *C. elegans* meiosis. The absence of chromosome movement, as observed in *mtf-1*/*sun-1(jf18)* mutants, results in a complete lack of presynaptic homologous alignment and the inappropriate establishment of a synaptonemal complex between non-homologous chromosomes, which ultimately prevents the establishment of crossovers. The matefin/SUN-1-mediated force might, therefore, not only be significant for bringing homologous chromosomes into close proximity (as a stirring force), but also for disrupting non-homologous contacts (as a repelling force).

Table 1 Summary of the known players that participate in the SUN-KASH interaction module responsible for meiotic chromosome movement in prophase I. See text for references.

Organism	SUN-domain protein	KASH-domain partner	Cytoplasmic motive force	Consequences of loss of rapid prophase movements (RPM)
S. cerevisiae	Mps3	N.D. (candidate: Mps2) (nuclear envelope protein Csm4 essential for chromosome movement)	actin cables	delay in homologue pairing; slight reduction of homologous associations; increased number of cross-over products; decreased cross-over interference; reduced non-cross-over frequencies; defects in the processing of recombination intermediates, e. g. inefficient second-end capture and timely resolution of double-Holliday junctions
S. pombe	Sad1	Kms1	microtubules actin-based forces?	delay in homologous pairing and in recombination increase of ectopic recombination
C. elegans	matefin/ SUN-1	ZYG-12	N.D.	absence of homologous alignment; non-homologous synapsis
Vertebrates	Sun1, Sun2	N.D.	N.D.	N.D.

Mammals

Although nuclear movements manifested as nuclear rotation or movements of chromosomes as a whole unit in meiotic prophase spermatocytes have been observed, it has not been experimentally addressed whether this movement involves the SUN-KASH interaction module. The movement was observed from late leptotene, reaching a peak in zygotene and slowing down in early pachytene. The microtubule drug colcemid inhibits this movement but at the same time damages the NE. It thus remains to be examined whether the effect of colcemid is exerted through microtubule poisoning [96–98], also reviewed in [99]. On the other hand, the meiotic KASH-domain partners of Sun1 and Sun2 have yet to be identified, although tissue culture experiments show that Sun1 and Sun2 can establish the nucleo/cytoplasmic link to Nesprin1 or Nesprin2, most likely building up a connection to the actin cytoskeleton [16, 80, 100, 101]. In summary, the above data suggest that chromosomes of meiotic prophase nuclei are moved by a highly conserved mechanism from outside the nucleus (Fig. 2). Driving forces originate from cytoplasmic structures such as actin or microtubule filaments. Although, depending on the organism, different motive forces are used, the molecular bridge that transmits the motive force across the NE to attached chromosome ends most likely involves the evolutionarily conserved SUN-KASH protein complexes, see table 1 for an overview and Fig. 2 for specific examples.

SUN-KASH domain proteins in disease

Mutations in the gene encoding human lamins A/C cause more than 12 distinct diseases, collectively termed laminopathies (reviewed in [7]). How mutations in lamins cause a wide variety of diseases is an intriguing unsolved question. There are several models that try to explain why mutations within the same gene (*LMNA*) cause so many different diseases which are not mutually exclusive [1]. One of these models takes into account that mutations in lamins cause abnormal lamin assembly that destabilizes the interactions between the nucleus and the different cytoskeletal networks, thus affecting mechanical properties of the cell [8]. Indeed, it recently became clear, that some of the pathology found in laminopathies is a direct result of a damaged link between the NE and the cytoskeleton. For example, there is a significant increase in the distance between the centrosome and the nucleus in mouse cells in which the *Lmna* gene has been replaced with a mutant *Lmna* gene ($Lmna^{L530P/L530P}$), a model for Hutchinson-Gilford progeria syndrome (HGPS). Similarly, in mice lacking lamin A/C ($Lmna^{-/-}$), a model for Emery-Dreifuss muscular dystrophy (EDMD) and cardiomyopathy, the centrosome is detached from the nucleus [102]. A repositioning of the centrosome is also seen in Nesprin-2-Giant knockout dermal fibroblasts [41]. $Lmna^{-/-}$ mouse embryonic fibroblasts (MEFs) display a slight, but significant, cell migration and a polarization defect in wound-healing *in vitro*. The elasticity and the viscosity of the cytoplasm were also reduced [103]. Lack of emerin, a lamin-binding protein that depends on lamins A/C for its NE localization, also causes the centrosome to detach from the nucleus (see above, [48]). Although no drastic changes were observed in the actin cytoskeleton of the $Emd^{-/y}$ MEFs, small, but significant changes were detected in actin-mediated cellular functions, including cell adhesion, cell migration, and cell mechanics [102]. Based on the assumption that mechanical properties and signals to the nucleus depend on the link between the nuclear

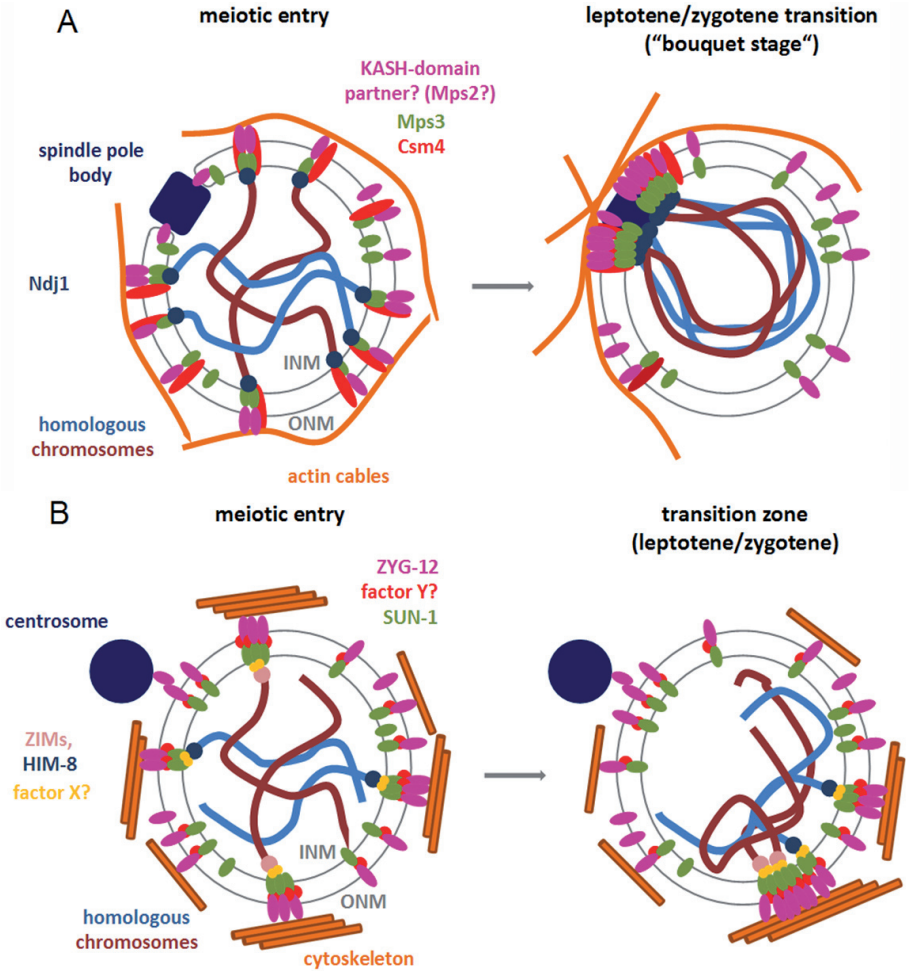

Figure 2. Examples of telomere-led chromosome movement in early meiosis in S. cerevisiae (A) and C. elegans (B). (A) Driving forces originate from cytoplasmic structures and are transmitted to the nucleus via SUN-KASH protein complexes (see text for detailed explanation). The localization of both chromosome ends to the nuclear envelope requires the meiosis-specific protein Ndj1 (blue circle) which interacts with the SUN-domain protein Mps3 (green ellipse). Cytoplasmic actin cables (orange line) move chromosomes (blue and brown line) in early meiosis, which leads to the formation of a telomere cluster in the vicinity of the spindle pole body (blue square). The participation of a KASH-domain partner (pink ellipse) in chromosome movement is still not clear, while Csm4 has unambiguously been shown to be involved in chromosome dynamics. (B) In C. elegans, the pairing center-end of each chromosome (blue and brown line) is anchored at the nuclear envelope by an unknown mechanism. Matefin/SUN-1 (green ellipse)-ZYG-12 (pink ellipse) form aggregates at sites of chromosome attachment. The cytoskeleton (orange line) involvement in the movement and clustering of meiotic chromosomes is yet to be defined.

lamina and cytoplasmic structures, it was assumed that the disruption of SUN-KASH protein complexes by mutations in lamins is most likely to be involved in the mechanism leading to many other laminopathies [8]. Another disease affecting the SUN-KASH protein complex is torsion dystonia (DYT1), a dominantly inherited movement disorder caused by mutations in torsinA. The torsinA protein is localized at the lumen of the NE and the endoplasmic reticulum (ER). It interacts with the KASH-domain of Nesprin-1, Nesprin-2 and Nesprin-3 *in vitro*. In the absence of torsinA, Nesprin-3 is displaced from the NE to the ER [104]. TorsinA-null MEFs have reduced polarization of nuclei relative to the centrosome, and delayed migration in wound-healing assays [104]. Thus, torsinA influences the localization of nesprins and association of cytoskeletal elements and affects their role in nuclear and cell movement.

The Nesprins are also directly involved in causing laminopathies. Screening 190 probands with EDMD or EDMD-like phenotypes identified 3 heterozygous missense mutations in Nesprin-1 and one in Nesprin-2 within the mapped emerin and lamin-binding domains [105]. Patient fibroblasts showed nuclear morphology defects and emerin and SUN2 were displaced from the NE. In addition, *in vitro* differentiation of myoblasts to myotubes was impaired in cells from patients with Nesprin-1 or Nesprin-2 mutations. Down regulation of Nesprin-1 or Nesprin-2 in normal fibroblasts caused nuclear morphological defects and displacement of emerin and SUN2, similar to what is observed in patient fibroblasts [105]. Taken together, the accumulating data strengthen the model that EDMD and potentially other laminopathies may be caused, in part, by uncoupling of the nucleoskeleton and cytoskeleton because of perturbed Nesprin/emerin/lamin interactions.

Interestingly, five autosomal recessive mutations in Nesprin-1, all predicted to cause premature translation termination, were mapped to French-Canadian families having recessive cerebellar ataxia type 1 (ARCA1) with pure cerebellar atrophy, also known as recessive ataxia of Beauce [106], making it the first identified gene responsible for a recessively inherited pure cerebellar ataxia. The mechanism leading to specific central nervous system defects in those

patients is still unclear. It would be important to determine whether other NE proteins and nuclear morphology are affected in cerebellar ARAC1 cells, since biopsies from ARCA1 individuals showed abnormal organization of neuromuscular junction, similar to the mice knockout for Nesprin-1. Sun1 knockout mice are sterile and have fewer germ cells (see above, [77]). However, there are still no data indicating SUN1 or SUN2 involvement in human fertility problems.

Mutations in LIS1 cause lissencephaly, a neurodevelopmental disease, in which neurons fail to properly migrate to the cortex [107]. NudF, the Aspergillus homologue of LIS1, is required for nuclear positioning [34], another function that normally requires SUN-KASH domain protein complexes. It would be interesting to test if Nesprin-1's functions in the cerebellum are mediated by LIS1 or whether LIS1 is involved in a different mechanism of nuclear migration.

In summary, it has become clear that mutations in SUN-KASH proteins cause human heritable diseases. SUN-KASH proteins also play a role in diseases caused by mutations in their binding partners. In some of these diseases, such as lissencephaly, which involves defects in nuclear positioning, the role of SUN-KASH proteins is yet unknown. A challenge for future studies will be to understand why mutations in the same proteins cause different diseases involving different tissues. Another challenge will be to find out what are the exact roles of SUN-KASH domain proteins in the pathogenesis of laminopathic diseases, including EDMD, caused by mutations in lamins A/C or in emerin.

Other functions for SUN-KASH domain proteins

In *S. pombe*, cytoplasmic microtubules are mechanically coupled to the heterochromatin through proteins of the NE [108]. Ima1, an integral INM protein, binds to heterochromatic regions and helps to tether centromeric DNA to the SUN-KASH complex of Sad1 and Kms2. Lack of Ima1 or lack of the functional centromeric Ndc80 complex causes detachment of heterochromatin from the NE, defects in the NE, including loss of round shape, ruffled NE and large extensions of the NE at the MT-NE interface. It also causes loss of spindle pole body components from the NE and partial dissociation of SUN-KASH complexes [108]. Thus, a network of integral membrane proteins and heterochromatin together establish a macromolecular linkage between the nuclear interior and the cytoplasmic cytoskeleton.

SUN- and KASH-domain proteins also have functions that have not been studied in detail. In *C. elegans*, mutations in the SUN-domain protein UNC-84, in addition to disrupting nuclear migration and anchorage, cause abnormal migration of the gonadal distal tip cells, egg laying defects and reduced fat levels [10]. These phenotypes were not observed in animals lacking the known KASH-domain partners, UNC-83 or ANC-1, suggesting that UNC-84 also has other binding partners [10]. ANC-1 is also expressed in mono-nucleated cells, and its function is required for anchoring the mitochondria. Actin filaments, but not UNC-84, are necessary to anchor the mitochondria [24].

Matefin/SUN-1 is detected in all embryonic cells until mid-embryogenesis and thereafter only in germline cells. Embryonic matefin/SUN-1 is maternally deposited, and *mtf-1/sun-1* was the first nuclear membrane gene known to have germline-restricted expression. It is required for embryogenesis because embryos fed with dsRNA of *mtf-1/sun-1* die around the ~300-cell stage with defects in nuclear structure, DNA content, and chromatin morphology [14]. Starting at the larva L2 stage, Matefin/SUN-1 is also required for germline proliferation or survival. The mechanisms behind matefin/SUN-1 functions in early embryos and during earlier stages of germline formation are not yet known.

In addition to its role in eye development, the *Drosophila* KASH-domain protein Klarsicht is required for developmentally regulated movements of lipid droplets in early embryos [109]. In an alternative spliced isoform, the KASH-domain of Klar is replaced with a domain called LD that binds lipid droplets [110]. One role of Klarsicht in this process is to link lipid droplets with the microtubule skeleton through dynein. Alterations in transport affect the motion in both apical and basal directions, indicating a tight coupling between motors of opposite polarity.

The mouse Nesprin-1 was also isolated in a yeast 2-hybrid screen of muscle-specific tyrosine kinase (MuSK). It is involved in the MAP kinase cascade at the neuromuscular junction of skeletal muscles [37]. In skeletal muscles, Nesprin-1 may also link the nucleus to the Golgi. Large Nesprin-1 isoforms have two Golgi binding sites that are found at the Golgi. Overexpression of Golgi binding sites containing Nesprin-1 fragments disrupts Golgi structure in cultured cells [111].

Nesprin-1 is also involved in cytokinesis. A non-spectrin repeat central fragment of Nesprin-1 interacts with the KIF3B subunit of the kinesin II motor. Overexpression of this fragment or the carboxyl terminus of KIF3B prevented cytokinesis. KIF3B and Nesprin-1 proteins are colocalized at the central

spindle and midbody during cytokinesis and this association could allow Nesprin-1 to attach vesicles to the kinesin motor protein, bringing extra membrane to the cleavage site to increase the surface area available for the formation of the two daughter cells [112]. Thus, in addition to anchoring the nucleus to actin, Nesprin-1 also tethers the nucleus to the Golgi in muscle cells, localizes protein complexes to the NE and is involved in cytokinesis.

In many cells, the cytoplasmic IF network is in close proximity to the nucleus. Nesprin-3A is a newly identified KASH-domain protein which localizes to the NE where it interacts with plectin [26]. Plectin, a plakin family member, consists of an actin-binding domain, an extended coiled-coil domain, and an IF-binding domain and can crosslink actin filaments to IFs [113]. The actin-binding domain can alternatively interact with other proteins including integrins. According to the suggested model [26], Nesprin-3 and plectin could together extend from the outer nuclear membrane into the cytoplasm to interact with IFs. Although recombinant KASH domains of Nesprins 1, 2 and 3 interact promiscuously with luminal domains of Sun1 and Sun2 in HeLa cells *in vitro* [101], it is not yet known which is the *in vivo* SUN-domain partner of Nesprin-3. It is worth noting that genes encoding KASH-domain proteins often also encode isoforms lacking KASH domains that do not target to the nuclear envelope, suggesting that the roles of these genes are still not fully understood (for review see [9]). In summary, the accumulating data suggest that SUN-KASH domain proteins have many functions other than nuclear positioning or linking of cytoskeletal networks to the nucleus. However, the role of the SUN-KASH domain proteins in these processes is still poorly understood.

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