

A network of nuclear envelope proteins and cytoskeletal force generators mediates movements of and within nuclei throughout *Caenorhabditis elegans* development

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Impact statement

Defects in nuclear positioning disrupt development in many mammalian tissues. In human development, LINC complexes play important cellular functions including nuclear positioning, homolog pairing in meiosis, DNA damage repair, wound healing, and gonadogenesis. The topics reviewed here are relevant to public health because defects in nuclear positioning and mutations in LINC components are associated with a wide variety of human diseases including muscular dystrophies, neurological disorders, progeria, aneurysms, hearing loss, blindness, sterility, and multiple cancers. Although this review focuses on findings in the model nematode *Caenorhabditis elegans*, the studies are relevant because almost all the findings originally made in *C. elegans* are conserved to humans. Furthermore, *C. elegans* remains the best described network for how LINC complexes are regulated and function.

Abstract

Nuclear migration and anchorage, together referred to as nuclear positioning, are central to many cellular and developmental events. Nuclear positioning is mediated by a conserved network of nuclear envelope proteins that interacts with force generators in the cytoskeleton. At the heart of this network are linker of nucleoskeleton and cytoskeleton (LINC) complexes made of Sad1 and UNC-84 (SUN) proteins at the inner nuclear membrane and Klarsicht, ANC-1, and Synne homology (KASH) proteins in the outer nuclear membrane. LINC complexes span the nuclear envelope, maintain nuclear envelope architecture, designate the surface of nuclei distinctly from the contiguous endoplasmic reticulum, and were instrumental in the early evolution of eukaryotes. LINC complexes interact with lamins in the nucleus and with various cytoplasmic KASH effectors from the surface of nuclei. These effectors regulate the cytoskeleton, leading to a variety of cellular outputs including pronuclear migration, nuclear migration through constricted spaces, nuclear anchorage, centrosome attachment to nuclei, meiotic chromosome movements, and DNA damage repair. How LINC complexes are regulated and how they function are reviewed here. The focus is on recent studies elucidating the best-understood network of LINC complexes, those used throughout *Caenorhabditis elegans* development.

Keywords: Nuclear envelope, linker of nucleoskeleton and cytoskeleton (LINC), nuclear positioning, cellular, nuclear, development

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Introduction

Nuclear positioning, which involves moving the nucleus to a specific intracellular location and anchoring it in place, is central to many cellular and developmental processes including pronuclear migration, cellular migration, muscle development, and neuronal differentiation.¹

Here I discuss the contributions to our current understanding of nuclear positioning and movements of and within nuclei made using *Caenorhabditis elegans* as a model. None of the findings presented here would have been possible without the foundational contributions made by John Sulston and his colleagues. Sulston's findings

include describing the developmental cell lineage and nuclear migration events in the embryo and larva,^{5,6} isolating the first mutants with nuclear positioning defects,^{12,13} and spearheading the effort to sequence the *C. elegans* genome¹¹ (Box 1).

Nuclear positioning requires closely regulated interactions between nuclei and the cytoskeleton. Thus, it is important to understand the nuclear envelope, which lies at the interface between the nucleus and the cytoskeleton.^{2–4} Connecting nuclei to the cytoskeleton is complicated by two characteristics of the nuclear envelope. First, the cytoplasmic face of the outer nuclear membrane needs to

Box 1 Sir John Sulston (1942–2018), a scientific giant of developmental biology.

New findings are made by “standing on the shoulders of giants” (Isaac Newton 1610). Our giant is John Sulston (1942–2018).^{7,8} Sulston, an early member of Sydney Brenner’s group that established *C. elegans* as a model organism in the 1970s, found that 15 nuclei in the ventral cord of a newly hatched larvae turned into 57 in the young adult. Sulston set out to determine where the cells came from during development. Surprisingly, he found that the original 12 cells did not divide; instead new cells (now known as P cells) “spontaneously appeared within the ventral cord”.⁹ These P-cell nuclei “were squeezing into the ventral cord from nearby positions out of the plane of focus”.^{6,9,10} The findings described in this review hailed directly from attempts to determine how P-cell nuclei squeeze into the ventral cord during development.

Sulston made at least three other major contributions that accelerated the field. In the seminal paper that led to his Nobel Prize,^{5,10} Sulston determined the entire cell lineage of the *C. elegans* embryo. While doing so, he described nuclear migrations in *hyp7* precursors on the dorsal surface of the embryo⁵ that has proven important for understanding nuclear migration in a live animal. Second, Sulston and Horvitz isolated the first alleles of *unc-83* and *unc-84* in a classic screen for lineage defects.^{12,13} Cloning *unc-83* and *unc-84* eventually led to the discovery of LINC complexes as described in this review. Finally, Sulston led teams sequencing the *C. elegans* genome.¹⁴ Part of that effort was to create a physical map of cosmids covering the *C. elegans* genome,¹¹ which allowed the cloning of genes, including *unc-83* and *unc-84*. This review is dedicated to the memory and honor of John Sulston, a true scientific giant.

be specifically marked as distinct from the contiguous, and much larger, endoplasmic reticulum (ER) membrane. A failure to designate the nuclear surface could lead to improper connections between the cytoskeleton and the ER. Second, once the outer nuclear membrane is distinguished from the ER, forces generated in the cytoplasm need to be transferred across both membranes and the perinuclear space of the nuclear envelope to structural elements in the nucleoskeleton. Finally, components specific to the inner nuclear membrane must connect the nuclear envelope to structural components in the nucleoplasm, including lamins and chromatin.^{15,16}

The discovery of *Sad1/UNC-84* (SUN) and *Klarsicht/ANC-1/Syne homology* (KASH) proteins,^{17–21} led to a model where SUN and KASH proteins form a bridge across the nuclear envelope to transfer mechanical forces generated by the cytoskeleton in the cytoplasm to structural elements inside nuclei.¹⁷ This model overcomes the two obstacles presented by the nuclear envelope.^{22,23} First, KASH proteins localize specifically to the outer nuclear membrane, but not the ER, specifically marking the surface of the nucleus. Second, SUN proteins in the inner nuclear membrane interact with KASH proteins in the outer nuclear membrane to form a physical bridge that transfers mechanical forces across both membranes of the nuclear envelope (Figure 1).

SUN-KASH bridges are broadly conserved and are now known as *linker of nucleoskeleton and cytoskeleton* (LINC) complexes,^{23–30} LINC complexes play many roles in addition to nuclear positioning. Foremost, they are thought to have been instrumental in the early evolution of eukaryotes.³¹ Additional examples of some of their many roles include meiotic homolog pairing,^{32,33} ciliogenesis,^{34,35} Golgi maintenance,³⁶ DNA damage repair,^{37,38} wound healing,³⁹ spermatogenesis,^{40,41} and nuclear pore complex formation.⁴² Not surprisingly, LINC complex defects are associated with a wide variety of human diseases including cardiomyopathies,^{43–46} hearing loss,⁴⁷

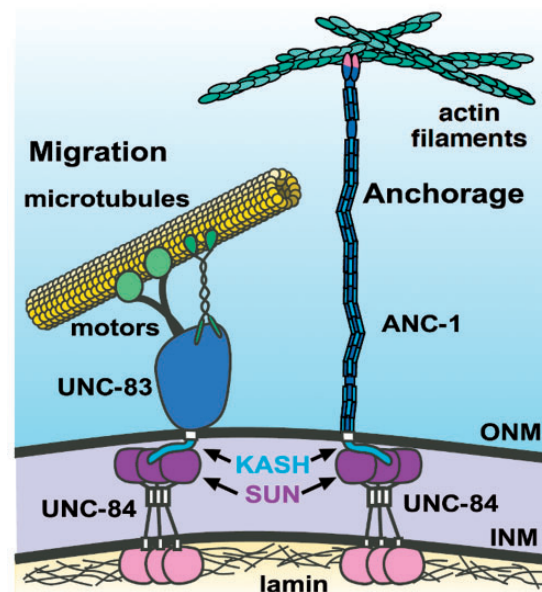


Figure 1. SUN trimers (UNC-84 in *C. elegans*) localize to the inner nuclear membrane. SUN domains (purple) recruit KASH proteins (blue) to the outer nuclear membrane. UNC-83 recruits microtubule motors to move nuclei along microtubules. ANC-1 potentially anchors nuclei to actin. See text for more details. (A color version of this figure is available in the online journal.)

blindness,⁴⁸ neurological disorders,^{49–52} progeria,^{53,54} sterility,⁵⁵ and various cancers.^{56–60}

Here, I focus on how LINC complexes are central to a conserved network of nuclear envelope proteins, effectors, and force generators that mediate nuclear positioning in *C. elegans* (Figure 2). *C. elegans* has two SUN proteins: the canonical UNC-84 (orthologous to mammalian Sun1 and Sun2) and the more divergent SUN-1. There are also four KASH proteins in *C. elegans*, ANC-1 (orthologous to Nesprin-1 and -2), UNC-83 (functionally related to mammalian Nesprin-4 and KASH5), ZYG-12, and KDP-1.²⁴ Herein I summarize the current literature on *C. elegans*

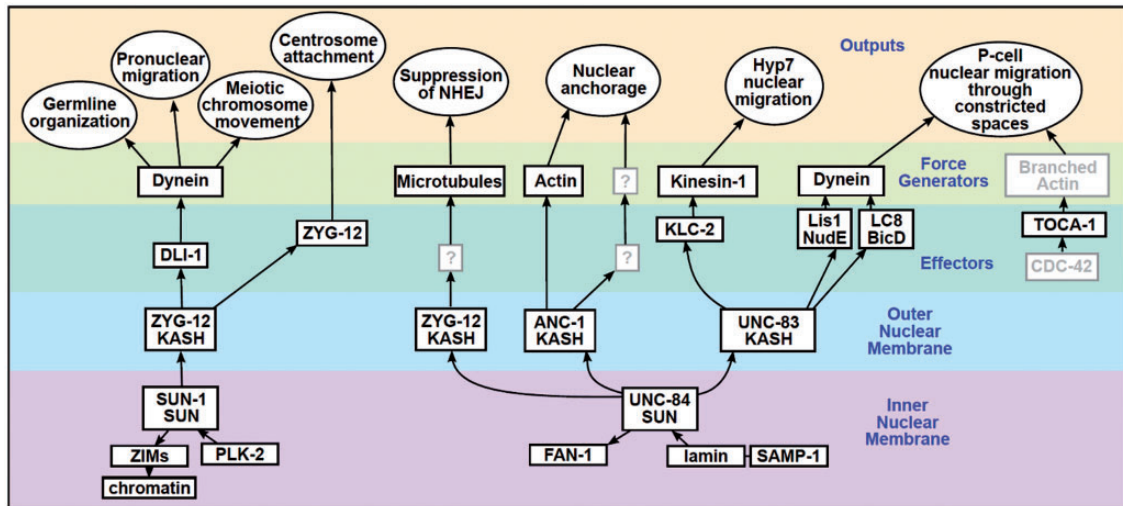


Figure 2. A network of LINC proteins and their functions at the nuclear envelope. A large, mostly conserved, network of *C. elegans* proteins regulates nuclear positioning and other functions throughout development. The purple layer contains SUN proteins and the proteins they interact with in the nuclear lamina. KASH proteins in the outer nuclear membrane are in the blue layer. The green layer contains the effectors that KASH proteins directly interact with. The yellow-green layer lists the cytoskeletal elements regulated by the KASH effectors. The cytoskeletal players then provide the mechanical forces to produce the cellular outputs listed in the top, orange layer. Unknown or hypothesized players are in gray. All black arrows are supported by genetic and/or biochemical evidence as described and referenced throughout the text. (A color version of this figure is available in the online journal.)

LINC complexes starting with what is known about the regulation of different LINC complexes and how LINC complexes maintain the architecture of the nuclear envelope. Next, I describe how SUN proteins interact with lamins and function in DNA damage repair. Turning to the cytoplasmic face of nuclei, I explain how LINC complexes mediate nuclear migration in developing hypodermal tissues, nuclear anchorage in adult hypodermal syncytia, and pronuclear migration in newly fertilized zygotes. I also write about the role of LINC complexes in rapid chromosome movements during meiotic prophase. Finally, I discuss how LINC complexes work with a branched actin network to squeeze nuclei squeeze through constricted spaces.

Interactions between SUN and KASH proteins to form LINC complexes

The central core of LINC complexes is the physical interaction between conserved domains of SUN and KASH proteins in the perinuclear space between inner and outer nuclear membranes.²³ LINC complexes have been proposed to maintain nuclear architecture; disruption of LINC in adherent HeLa cells, which are under considerable mechanical strain to spread across the tissue culture plate,⁶¹ results in large blebs between the inner and outer nuclear membranes.⁶² The role of LINC complexes in maintaining nuclear envelope architecture was tested in *C. elegans* tissues using electron microscopy in *unc-84* null (SUN) mutants. Surprisingly, nuclear envelope architecture was normal in most embryonic and larval tissues, suggesting that LINC is not required to maintain the even spacing of nuclear membranes.⁶³ The exception was in larval body-wall muscles, where the outer nuclear membrane was pulled from about 40 to 500 nm from the inner nuclear membrane.⁶³ Nuclear envelope defects correlate with

movement defects in *C. elegans* L1 larvae,⁶³ suggesting that nuclear envelope morphology might play a role in muscular pathologies. These findings suggest LINC complexes are required to maintain nuclear envelope architecture, but only in tissues subjected to mechanical strain.⁶⁴

A major breakthrough in our mechanistic understanding of how LINC complexes function occurred when the structure of mammalian SUN–KASH interfaces was determined.^{65,66} Crystal structures revealed that three KASH peptides interact with a trimer of SUN proteins and that each KASH peptide forms three interfaces with SUN protomers. The four C-terminal residues of KASH interact with a pocket of the first SUN protomer. The next 11 residues fit into a cleft between two SUN protomers. Finally, the next 10 residues interact with the surface of the second protomer. At residue -23 from the C terminus of KASH, a conserved cysteine forms a disulfide bond with a conserved cysteine in SUN. Thus, the interactions between SUN and KASH are predicted to be stable and able to transmit mechanical forces across the nuclear envelope.^{25,65,67}

Genetic approaches in *C. elegans* are ideal to test functional consequences of predictions raised by the SUN/KASH structure. *C. elegans* somatic cells have two major LINC complexes—UNC-83 and UNC-84 move nuclei, while ANC-1 and UNC-84 anchor nuclei in place (Figure 1). Yet, little was known about how the UNC-84 SUN protein is regulated to interact with different KASH proteins. One major difference between UNC-83 and ANC-1 KASH domains is that ANC-1 has a full-length KASH domain with all three interaction interfaces and the conserved cysteine at the -23 position,^{21,68} but UNC-83 has a truncated KASH (only 18 residues long) that lacks the third interaction interface and the conserved cysteine.^{68,69} *In vivo* functional analyses of point mutations predicted to disrupt SUN–KASH interactions showed that extending the C terminus of the UNC-83 KASH domain by a single alanine

blocks nuclear migration.⁶⁸ Additionally, mutations of a conserved aromatic amino acid seven residues from the C terminus of KASH cause intermediate nuclear positioning phenotypes. The UNC-83(Y-7A) mutant interacts with SUN well enough to localize to the nuclear envelope but not strongly enough to mediate nuclear migration. In contrast, the ANC-1(F-7A) mutant had no effect on nuclear anchorage.⁶⁸ Thus, the structure of SUN-KASH interactions led to predictions for how LINC complexes behave that were tested *in vivo*.

The intermolecular disulfide bond between SUN and KASH identified in the crystal structure hints at a difference in the regulation of how SUN might choose between KASH partners. The conserved cysteine at residue -23 is present in the nuclear anchorage KASH protein, ANC-1, but not in the nuclear migration KASH protein, UNC-83 (Figure 1). Thus, intermolecular cysteine bonds were hypothesized to be important for nuclear anchorage, but dispensable for nuclear migration.^{68,70} Mutating conserved cysteines in SUN or KASH disrupted ANC-1-dependent nuclear anchorage, but not UNC-83-mediated nuclear migration.⁶⁸ Click or tap here to enter text. Furthermore, molecular dynamic simulations showed that SUN-KASH pairs lacking intermolecular disulfide bonds could not transmit as much force as wild-type LINC complexes.⁶⁸ To further test this model, the KASH domains of ANC-1 and UNC-83 were swapped.⁷¹ ANC-1 with the short KASH from UNC-83 partially blocked nuclear anchorage, while UNC-83 with the long ANC-1 KASH had a partial nuclear migration defect. Mutation of the cysteine in the UNC-83 with the long ANC-1 KASH construct completely blocked nuclear migration, suggesting that short KASH domains are able to transfer more forces across LINC complexes than long KASH domains missing the intermolecular disulfide bonds.⁷¹ Thus, the length of KASH domains and their ability to form intermolecular disulfide bonds with SUN partners contributes to the ability of LINC complexes to transfer forces across the nuclear envelope.

LINC complexes interact with lamins and contribute to DNA damage repair

LINC complexes function like a bolt through the nuclear envelope.^{72,73} A bolt through a planar surface without a nut or washer on the other side will likely fail when forces are applied to the bolt. The washer and nut serve to dissipate the forces transferred by the bolt, stabilizing the system. In this analogy, the nuclear scaffold, made of lamins, inner nuclear membrane proteins, and associated complexes, serves as the washer to dissipate mechanical forces generated in the cytoplasm. UNC-84 is recruited to the inner nuclear membrane where it is retained by the sole *C. elegans* lamin, LMN-1.^{72,74-76} Specifically, the nucleoplasmic domain of UNC-84 interacts with LMN-1 in a two-hybrid assay and this interaction is significantly weaker in the presence of an *unc-84(P91S)* mutation.⁷² Interestingly, the *unc-84(P91S)* allele was originally found as an intermediate disrupter of nuclear migration.²⁰ Live imaging showed that 62% of nuclei in the *unc-84(P91S)* background migrated normally, 22% started migration

normally, but stopped before completion, and 16% failed to initiate migration.⁷² Consistent with this bolt and nut model, *lmn-1(RNAi)* animals also have a nuclear migration defect⁷² and human SUN proteins interact with Lamin A.⁷⁷ Based on the literature in mammalian cells and fission yeast, the inner nuclear membrane protein NET5/SAMP/Ima1 interacts with LINC complexes and is thought to participate with LINC to help dissipate forces on the nucleoskeleton.^{73,78} The *C. elegans* homolog SAMP-1 also localizes to the nuclear membrane and knockdown of *samp-1* leads to weak nuclear migration defects.⁷² Thus, LINC complexes interact with the nucleoskeleton to mediate nuclear migration.

LINC complexes are used to move chromosomes within nuclei and have been recently implicated in the DNA damage response.^{38,79} SUN proteins promote homologous recombination by inhibiting non-homologous end joining (NHEJ).³⁷ Specifically, *unc-84* mutants and human cells depleted of Sun1 were both hypersensitive to DNA cross-linking, which was rescued by inactivating NHEJ. UNC-84 also recruited Fanconi anemia nuclease, FAN-1, to the nucleoplasm of germ line nuclei,³⁷ suggesting that UNC-84 alters both the extent of repair by NHEJ and promotes processing of DNA crosslinks. The KASH protein ZYG-12 and microtubules are also required.³⁷ This suggests that LINC complexes play a conserved role in DNA repair through both the inhibition of NHEJ and the promotion of homologous recombination.

UNC-84/UNC-83 LINC complexes recruit microtubule motors to move nuclei in somatic tissues

KASH proteins are positioned on the cytoplasmic surface of the nuclear envelope where they can interact with a variety of different cytoskeletal modules.^{24,80} The KASH protein UNC-83 interacts with microtubule motors to move nuclei. A yeast two-hybrid screen with the cytoplasmic domain of UNC-83 identified interactions between UNC-83 and four regulators of microtubule motors: the kinesin light chain KLC-2, and the dynein regulators NUD-2 (NudeE homolog), BICD-1 (bicaudalD homolog), and DLC-1 (an LC8 dynein light chain).^{81,82} Knockdown of the kinesin-1 motor caused a severe nuclear migration defect in embryonic *hyp7* precursors, but knockdown of dynein components only caused weak nuclear migration defects.^{81,82} This suggested that kinesin-1 is the major force producer to move nuclei, while dynein plays a regulatory role. Live imaging of the growing plus ends of microtubules showed that embryonic *hyp7* nuclei migrate toward plus ends of microtubules, consistent with the model that kinesin-1 is the major force producer.⁸³ Further live imaging showed that dynein was required for backward nuclear movements to move past cellular roadblocks.^{83,84} Thus, the role of UNC-83 during embryonic *hyp7* nuclear migration is to recruit kinesin-1 and dynein to the nuclear envelope, which then move nuclei towards the plus ends of microtubules. Mammalian KASH proteins Nesprin-1, Nesprin-2, Nesprin-4, and KASH5 also interact with microtubule motors.⁸⁵⁻⁸⁸ Although it is not possible to say which one of these KASH proteins is the UNC-83

ortholog, the role of KASH proteins recruiting motors to the surface of nuclei appears conserved.

The UNC-84/UNC-83 LINC complex is also responsible for nuclear migration in larval hypodermal P cells.^{12,13,17,20,89} P-cell nuclei migrate through a constricted space (discussed below). Surprisingly, P-cell nuclei migrate toward the minus ends of microtubules.⁹⁰ Furthermore, genetic analyses showed that dynein is the major motor required to move P-cell nuclei and that kinesin-1 plays a regulatory role.^{90,91} Thus, UNC-83 favors kinesin-1 in embryonic hyp7 precursors but prefers dynein in larval P cells. How UNC-83 dictates the choice between plus and minus-end directed microtubule motors remains an open question.

UNC-84/ANC-1 LINC complexes anchor nuclei in syncytial cells

After nuclei migrate to specific intracellular locations, they must be anchored in place. Mutations in the KASH protein ANC-1 or the SUN protein UNC-84 disrupt nuclear anchorage.^{20,21,92} ANC-1 is a giant protein of over 8500 amino acids. The C terminus of ANC-1 has a KASH domain, while the N terminus of ANC-1 contains two calponin homology domains that bind actin filaments *in vitro*.²¹ In between are extensive repeats predicted to be helical. ANC-1 is orthologous to mammalian Nesprin-1 and -2 and *Drosophila* MSP-300, all of which contain calponin homology domains and KASH domains at the ends, separated by long repetitive regions.^{21,23}

Nuclear anchorage defects are most easily observed in *C. elegans* syncytial cells, where normally evenly spaced nuclei are instead clustered together.⁹² The *C. elegans* adult hyp7 syncytium contains 139 nuclei that are normally uniformly spread throughout the length of the animal. In *anc-1* or *unc-84* mutants, syncytial hypodermal nuclei are frequently seen in abnormal clusters.^{20,21,92} The phenotype and molecular identity of ANC-1 led to the current model, where ANC-1 directly tethers nuclei to the actin cytoskeleton to anchor nuclei in place.²¹

More recent data suggest that the tethering model for ANC-1 is overly simplistic. This working model predicts that null mutations in *anc-1* or *unc-84* should have similar phenotypes, as both would equally disrupt the LINC complex. However, a careful quantification of the nuclear anchorage phenotype⁹³ shows that null mutations in *anc-1* have much more severe nuclear anchorage defects than null mutations in *unc-84*.⁶⁸ This suggests that ANC-1 anchors nuclei through multiple mechanisms. First, the KASH domain of ANC-1 forms a LINC complex with UNC-84 to mediate interactions between nuclei and unknown cytoskeletal components. Second, the large cytoplasmic domain of ANC-1 functions in LINC-independent mechanisms for nuclear anchorage. One possibility is that ANC-1 mediates the formation of a microtubule cage, similar to what has been seen for the mechanism of MSP-300 in *Drosophila* muscles.⁹⁴ Further investigations are required to fully understand how ANC-1 functions to anchor nuclei.

SUN-1/ZYG-12 LINC complexes mediate pronuclear migration in the early embryo and organization of the germline

The first nuclear migration event in animals occurs in the newly fertilized zygote when male and female pronuclei migrate toward each other. In most animals, centrosomes are contributed by sperm and remain attached to the male pronucleus, while the microtubule motor dynein mediates female pronuclear migration toward the male pronucleus at the center of the microtubule aster.⁹⁵ LINC complexes consisting of the SUN protein SUN-1 and the KASH protein ZYG-12 are required for pronuclear migration in the early embryo and for organization of the germline.^{96,97} Because SUN-1 is divergent from other SUN proteins⁹⁸ and because the KASH domain of ZYG-12 is short and not well conserved with other KASH peptides,^{96,99} I refer to SUN-1/ZYG-12 as a non-canonical LINC.

SUN-1 and ZYG-12 were first identified because they cause a severe separation between centrosomes and the male pronucleus in the newly fertilized zygote.⁹⁶ There are two isoforms of ZYG-12; the KASH-less isoform localizes to centrosomes and the long isoform, which contains a C-terminal KASH domain, localizes to the nuclear envelope in a SUN-1-dependent manner to form a LINC complex.¹⁰⁰ KASH-less and full-length ZYG-12 then dimerize to attach centrosomes to the male pronuclear envelope. In *zyg-12* or *sun-1* mutants, both centrosomes become detached from the male pronucleus, leading to severe pronuclear migration defects.⁹⁶ ZYG-12 also interacts with the minus-end directed microtubule motor dynein through DLI-1.⁹⁶ SUN-1/ZYG-12 LINC complexes recruit dynein to the cytoplasmic surface of pronuclei. This allows male pronuclei to capture centrosomes shortly after fertilization.⁹⁶ Sperm nuclei are extremely compact and failure to expand rapidly after fertilization leads to a phenotype where a single centrosome is detached, suggesting that the surface area of the male pronucleus is important for centrosomal attachment.⁷⁵ Finally, SUN-1 and ZYG-12 are required to recruit dynein to female pronuclei to mediate pronuclear migration.⁹⁶

SUN-1 and ZYG-12 also interact with microtubules to organize nuclei in the *C. elegans* germline. Normally, during meiosis, germline nuclei are localized to the periphery of the syncytial gonad, evenly spaced and surrounding a nuclear-free rachis.^{101,102} In *zyg-12* mutant gonads, microtubules are disorganized, and nuclei fall into the rachis.⁹⁷ Thus, SUN-1/ZYG-12 LINC complexes are required to position nuclei in the germline and early embryo. In zebrafish and likely human embryos, Lrmp1/KASH5 plays an analogous role to ZYG-12, recruiting dynein to nuclei to mediate pronuclear migration.^{88,103}

LINC complexes move meiotic chromosomes to enable homologous chromosome pairing

Homologous chromosome pairing is one of many important events that occurs during meiotic prophase. Chromosome pairing occurs during a burst of rapid prophase movements driven by telomeres moving along the inner surface of the nuclear envelope. These movements are

thought to prevent non-homologous chromosomes from becoming interlocked.¹⁰⁴ LINC complexes in fission yeast were found to transfer forces generated by dynein in the cytoplasm, across the nuclear envelope, to meiotic telomeres, leading to rapid chromosome movements.¹⁰⁵ Subsequently, LINC complexes have been shown to mediate meiotic chromosome movements in plants and animals.^{32,33,106}

In *C. elegans*, LINC complexes of SUN-1 and ZYG-12 are required during homologous chromosome pairing.¹⁰⁷⁻¹⁰⁹ SUN-1/ZYG-12 LINC complexes transition from an even distribution around the nucleus in interphase to distinct puncta in the nuclear envelope that move throughout early meiotic prophase in conjunction with rapid chromosome movements.^{110,111} *C. elegans* LINC complexes interact with pairing centers, subtelomeric repeats, of meiotic chromosomes. The ZIM/HIM proteins mediate interactions between pairing centers and LINC complexes, although how LINC complexes directly interact with meiotic chromosomes is unknown.^{112,113} Lamins play a significant role in meiotic chromosome pairing. The *C. elegans* lamin LMN-1 is remodeled during rapid chromosome movements in meiotic prophase. LMN-1 is reduced and more sensitive to detergent, making it more soluble, allowing rapid chromosome movements.^{114,115} LMN-1 remodeling is regulated by CHK-2 and PLK-2 kinase activity; a phospho-mutant *lmn-1* animal, with eight phosphorylation sites mutated, was resistant to detergent and led to significant delays in homolog pairing.¹¹⁵ Additionally, the nucleoplasmic domain of SUN-1 is phosphoregulated by CHK-2 and PLK-2 during rapid chromosome movements. SUN-1 remains phosphorylated until homologous chromosomes are paired. Blocking SUN-1 phosphorylation leads to chromosome entanglements, unpaired chromosomes, and embryonic lethality.¹¹⁴⁻¹¹⁶ Thus, both LMN-1 and SUN-1 are regulated by kinases to facilitate rapid chromosome movements and homolog pairing in meiosis.

Migration of nuclei through constricted spaces

Cellular migrations through constricted spaces are a critical aspect of many developmental and disease processes including hematopoiesis, inflammation, and metastasis.^{3,117} Multiple labs have developed *in vitro* assays to observe cancer or dendritic cells migrating through narrow constrictions and have found that the stiffness of the nucleus is the rate-limiting step for such cell migrations.^{118,119} An *in vivo* model where nuclei can be observed moving through constricted spaces is needed to fully understand nuclear squeezing through constricted spaces. Thus, *C. elegans* larval P cells were developed as a model because their nuclei undergo extreme morphological changes to squeeze through a space about 5% their resting width as a part of normal development.⁹⁰

P-cell nuclear migration requires *unc-83* and *unc-84*. In fact, screens for mutants with P-cell nuclear migration defects led to the isolation of the first *unc-83* and *unc-84* alleles (see Box 1).^{12,13} Because UNC-83 recruits both kinesin-1 and dynein to the surface of nuclei in other

cells,⁸¹⁻⁸³ it was proposed that LINC complexes made of UNC-83 and UNC-84 would also mediate P-cell nuclear migration by serving as a cargo adaptor for microtubule motors. P-cell nuclei move toward the minus ends of microtubules.⁹⁰ This is in contrast to embryonic hyp7 precursors, described above, where nuclei migrate toward the plus ends of growing microtubules.⁸³ In support of P-cell nuclei moving toward the minus end of microtubules, genetic analyses showed that dynein is the major force producer and kinesin-1 plays an unknown regulatory role.^{90,91} Thus, LINC works through dynein to move nuclei through constricted spaces. How UNC-83 favors kinesin-1 in embryonic hyp7 nuclear migration but dynein in P-cell nuclear migration remains an open question.

Using LINC complexes is not the only mechanism mediating P-cell nuclear migration through constricted spaces. Null alleles of *unc-83* or *unc-84* are temperature sensitive.¹³ At restrictive temperatures, about 50% of P-cell nuclei fail to migrate, leading to P-cell death. Mutant animals are egg-laying deficient (Egl) because of missing vulva cells and uncoordinated (Unc) due to missing neurons normally derived from P-cell lineages. However, at permissive temperatures, almost all P-cell nuclei migrate in the absence of LINC complexes.^{17,20,89} This suggested that other pathways are sufficient to move P-cell nuclei through constricted spaces in the absence of LINC.

To identify proteins involved in this alternative P cell nuclear migration pathway, a forward genetic screen was carried out for enhancers of the *unc-84* nuclear migration defect.¹²⁰ *toca-1* was the first gene identified.¹²⁰ Transducer of Cdc42-dependent actin assembly (TOCA-1) contains an F-BAR domain thought to bind curved membranes, a predicted Cdc42-interacting domain, and a domain proposed to interact with WASP/WAVE to nucleate actin filaments.^{120,121} TOCA-1 and its close ortholog TOCA-2 function redundantly to play an essential role in endocytosis,¹²² but only TOCA-1 functions to facilitate P-cell nuclear migration.¹²⁰ It is likely that TOCA-1 and CDC-42 are regulating a branched actin network to help squeeze nuclei through constricted spaces. Branched actin networks are also thought to help dendritic cells move through small glass capillary tubes,^{118,123} suggesting a conserved mechanism. Elucidation of other players in the LINC-independent pathway will lead to a better understanding of how branched actin functions in P-cell nuclear migration.

Future directions

The network of LINC complexes, their effectors at the surface of nuclei, and the ways they interact with the cytoskeleton are better understood in *C. elegans* than in any other multi-cellular system. Most of what has been found in *C. elegans* has been conserved at a functional level in other animal systems, demonstrating its value as a model. Many questions must still be addressed in order to fully understand LINC networks. *C. elegans* continues to be well suited to address the following remaining gaps in the LINC field: (1) We do not fully understand how interactions between SUN and KASH proteins are regulated or how SUN proteins are prevented from interacting with KASH

proteins until they are trafficked from the peripheral ER to the inner nuclear membrane. (2) The recent finding that *anc-1* mutants have a much more severe nuclear anchorage phenotype than *unc-84* mutants⁶⁸ Click or tap here to enter text. suggests that the giant cytoplasmic domains of ANC-1 function through unknown mechanisms. (3) It remains unknown how the KASH protein UNC-83 favors kinesin-1 or dynein in different nuclear migration events. (4) Our understanding of how LINC complexes mediate DNA damage repair and gene regulation is still in its infancy. (5) How LINC complexes work with other mechanisms, including branched actin networks and other means of softening the nucleoskeleton, to squeeze nuclei through constricted spaces warrants further investigation. Furthermore, how LINC complexes relate to human health and disease progression is poorly understood. Answering these open questions and more will require many more years of research on the mechanisms and regulation of LINC complexes.

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