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Nuclear envelope: positioning nuclei and organizing synapses

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Abstract

The nuclear envelope plays an essential role in nuclear positioning within cells and tissues. This review highlights advances in understanding the mechanisms of nuclear positioning during skeletal muscle and central nervous system development. New findings, particularly about Atype lamins and Nesprin1, may link nuclear envelope integrity to synaptic integrity. Thus synaptic defects, rather than nuclear mispositioning, may underlie human pathologies associated with mutations of nuclear envelope proteins.

Keywords

Lamin; Nesprin; LINC complex; laminopathies; nuclear envelope; interkinetic nuclear migration; neuromuscular junction; retina; ribonucleoparticles

Introduction

The nuclear envelope (NE) consists of an inner nuclear membrane (INM) and an outer nuclear membrane (ONM) that enclose the perinuclear space (PNS). The NE is spanned by modular supramolecular structures, named Linkers of Nucleoskeleton and Cytoskeleton (LINC) complexes. LINC complexes were originally identified in seminal forward genetic studies in *C. elegans* that demonstrated their essential role in nuclear positioning within the cell [1–3]. LINC complexes assemble through direct interactions between Sun proteins and Nesprins (Nuclear envelope spectrin-repeat proteins), two families of transmembrane proteins that respectively populate the INM and ONM (Figure 1), via their evolutionarily conserved SUN (Sad1/Unc-84) and KASH (Klarsicht/Anc-1/Syne homology) domains. Within the nucleoplasm, the N-terminal region of Sun proteins interacts with the nuclear lamina, a meshwork of Type-V intermediate filaments that adjoins the INM [4]. In the cytoplasm, Nesprins collectively interact with all major cytoskeletal components. Hence SUN/KASH interactions mechanically couple cytoskeletal and nucleoskeletal structures [5–7]. The structural organization, diversity and function of LINC complexes in different

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cellular settings are covered in several excellent reviews [8–14]. This article will highlight new findings about NE-mediated positioning of the nucleus during central nervous system (CNS) development and skeletal muscle development, and a novel pathway for ribonucleoprotein (RNP) particle transport across the NE that may underlie the pathology of human laminopathies in unexpected ways. We begin by describing two distinct types of nuclear movement during CNS development: interkinetic nuclear migrations in dividing neural progenitors, and nuclear translocation in post-mitotic neurons.

Interkinetic nuclear migration

During CNS development, a pseudostratified neuroepithelium of cycling progenitors is transformed into distinct layers of differentiated neurons. This early and essential stage of development is accompanied by nuclear oscillations, known as interkinetic nuclear migrations (IKNM), in phase with the neuroepithelial cell cycle [15–19] (Figure 2A). During IKNM, nuclei migrate in a saltatory fashion towards the basal side of the neuroepithelium during G1-phase, then move rapidly back towards the apical side during G2-phase [20]. As a result, nuclei undergo S-phase at the basal side, and mitosis near the apical side of the cell (Figure 2A). Remarkably, the centrosome remains relatively stationary on the apical side during these oscillations [21,22] and may actually be dispensable for IKNM as recently demonstrated in zebrafish retina [23]. IKNM requires kinesin and dynein motors in the developing rat neocortex. It also requires myosin II in zebrafish retinal progenitor cells (RPCs) and in a region of the embryonic mouse brain known as the telencephalon [24,25]. LINC complexes, which couple the NE to molecular motors, seemed ideal candidates to mediate IKNM [26]. Further experiments, however, suggested a limited involvement. In developing retina from *Nesprin2* knockout (KO) and *Sun1/Sun2* double-KO (DKO) mice, only a few mitotic figures mislocalized within the neuroblast layer, and the number of retinal progenitor cells (RPCs) in S-phase was only slightly increased in *Nesprin2* KO retina [27]. Time-lapse recording of IKNM in *Sun1/Sun2* DKO and *Nesprin1/Nesprin2* DKO embryonic brain slices revealed a significantly reduced frequency of nuclear oscillations, over shorter distances, within neural progenitors [28]. By contrast, IKNM proceeded normally in E20 neural progenitors that expressed RFP-KASH, which dominantly disrupts all LINC complexes, suggesting that LINC complexes are dispensable for IKNM in developing rat cerebral cortex [29]. These authors elegantly demonstrated that apical nuclear migration during G2-phase is a two-step process requiring the sequential recruitment of dynein first to the NPC protein RanBP2/BicD2, and then to Nup133/CENP-F [29]. Inhibiting either step severely disrupted IKNM. The relatively mild effects of LINC complex disruption during IKNM are consistent with the puzzlingly near-normal eye development in KASH-mutated *Drosophila* (*klar;msp-300*) [30]. Furthermore, genetic ablation of *asp*, which plays a central role in IKNM by controlling the apico-basal distribution of Myosin II, drastically affects *Drosophila* eye morphology [31]. By contrast, in zebrafish retina, disruption of LINC complexes severely affects IKNM and decreases populations of late-born neurons in agreement with a role for IKNM in Zebrafish neurogenesis [32,33]. In summary, with the notable exception of the zebrafish retina, current evidence suggests that LINC complex disruption has only marginal, if any, effect on IKNM.

Nuclear translocation within post-mitotic neurons: major roles for LINC complexes

Exit of neural progenitors from the cell cycle triggers the migration of post-mitotic neurons from the apical side of the neuroepithelium toward their final laminar position (Figure 2B). In the developing cerebral cortex, migration of newborn cortical neurons from the apical (ventricular) side towards the basal (pial) surface requires active translocation of the nucleus [34]. By contrast to IKNM, this translocation is coupled to concerted forward movement of the centrosome, which ‘drags’ the nucleus using a fork-like array of microtubules. The dynein/dynactin complex, LIS1 and other microtubule-binding proteins [34–37], and LINC complexes are essential to couple centrosomes with nuclei. Indeed, in the developing cerebral cortex of *Nesprin2* KO or *Sun1/Sun2* DKO embryos, the centrosome still moves towards the pial surface, but nuclei remain stationary on the ventricular side. As a result, cortical lamination and CNS development are both severely impaired in E18.5 mutant embryos [28]. Thus LINC complexes have essential roles in early development of the cerebral cortex (Table I). Cortical lamination defects are also seen to differing extents in mice that lack lamin B1 and/or lamin B2 [38–41], further suggesting that forces exerted on LINC complexes during nuclear translocation are transmitted to the nuclear lamina of newborn cortical neurons.

LINC complexes appear dispensable for nuclear translocation in other neuronal precursors. In mouse retina, retinal ganglion cells (RGC) precursors are among the first post-mitotic cells to migrate towards the basal side of the retina, as early as E11 (Figure 2B). They subsequently extend long axons whose bundling forms the optic nerve. Disruption of LINC complexes does not appear to affect the embryonic migration of RGC, since nuclei of adult RGCs localize normally in both *Nesprin2* KO and *Sun1/Sun2* DKO mice [27]. Interestingly, whereas the centrosome clearly leads translocating nuclei in cortical newborn neurons, it localizes on the side or even behind translocating nuclei in migrating zebrafish RGCs and migrating cerebellar granule cell precursors *in vivo* [42,43].

Together, these results suggest LINC complexes are primarily involved in centrosome-mediated nuclear translocations, where mechanical forces are exerted by kinesin-1 and dynein whose direct interactions with KASH proteins are conserved in evolution [28,44–47]. Actin networks may also contribute to this force, since an actin-dependent pathway acts in parallel with SUN/KASH interactions to move nuclei in *C. elegans* [48]. Interestingly, actin ‘caps’ and transmembrane actin-associated nuclear (TAN) lines both correspond to contractile actin filaments that lie atop the nucleus of mammalian cultured cells and require LINC complexes for their formation [49,50]. Whereas TAN lines appear to be transient structures that mediate nuclear movements during cell polarization, actin caps form above nuclei of many cell types during persistent 2D migration and extend perinuclear membrane protrusions during 3D migration [51,52]. For these reasons, a careful examination of perinuclear actin filaments during nuclear translocation at early stages of CNS development may reveal previously-unrecognized functions of LINC complexes *in vivo*.

The postnatal differentiation of cone photoreceptors, born early in embryonic retinogenesis, provides another example of nuclear positioning controlled by LINC complexes *in vivo*.

Nuclei of cone precursors are scattered within the postnatal retina for several days before assuming apical positions beneath photoreceptor inner segments (Figure 2C; WT panel) [53]. The centrosome, whose mother centriole gives rise to the photosensitive outer segment, remains on the apical side. In *Nesprin2* KO and *Sun1* KO retina, cone nuclei partially mislocalize across the adult photoreceptor layer [27]. This phenotype is cell-autonomous, since EGFP-KASH expression under the control of a cone-specific promoter causes EGFP-KASH⁺ cone nuclei to completely mislocalize on the basal side of adult photoreceptor layers (Table I and Figure 2C; EGFP-KASH⁺ panel). This basal mislocalization further indicates that LINC complexes mediate the apical ‘leg’ of cone nuclei migration [54]. LINC complexes, nuclear lamina and motor proteins have evolutionarily conserved roles in the positioning of cone cell nuclei, since similar phenotypes are reported in *Drosophila klarsicht* (*Nesprin*), *klaroid* (*Sun*), *lamDm0* (B-type lamins) and *glued* (dynactin) mutants [55–57], and in zebrafish *mok* (dynactin) mutants [58].

Nuclear positioning in skeletal muscle

KO mouse models of *Nesprin1* and *Nesprin2* (aka *Syne1* and *Syne2*) were derived by partial ablation of their respective KASH domains [59]. These mice develop normally with no overt phenotype, but revealed specific roles for *Nesprin1* in the anchoring of synaptic myonuclei beneath arrays of acetylcholine receptors at the NMJ (Figure 3, Box 1), and in the spacing of extrasynaptic nuclei along muscle fibers. These functions are conserved in evolution, since genetic ablation of the KASH domain of either *msp-300* or *klar*, both of which encode Nesprin orthologs in *Drosophila*, causes myonuclei mispositioning and abnormal muscle morphogenesis [60–62]. Unlike Klar, which localizes nearly exclusively at the NE in myonuclei, MSP-300 also localizes at Z-discs and forms perinuclear rings [60]. A similarly complex distribution was reported for Nesprin1 and Nesprin2 in sarcomeres of human and mouse skeletal muscle [63,64]. Consistent with the Sun-dependent anchoring of Nesprins at the ONM [7,65,66], synaptic nuclei were partially mislocalized in *Sun1* and *Sun2* KO mice, and were virtually “wiped out” from the NMJ, with extensive clustering of extrasynaptic nuclei, in *Sun1/Sun2* DKO muscle fibers [67]. Similarly, because lamins anchor Sun proteins at the nuclear envelope [66,68,69], myonuclear mispositioning is also observed in *Lmna*^{−/−} and *Lmna*^{H222P/H222P} mice [70]. Together, these data reinforce the importance of LINC complexes and A-type lamins in myonuclei positioning.

Nuclear envelopathies and ribonucleoparticle trafficking across the nuclear envelope

Several studies have suggested that nuclear mispositioning is not clinically relevant in muscle. For example, nuclear mispositioning is a common feature of *Nesprin1* KO, *Lmna*^{−/−} and *Lmna*^{H222P/H222P} mouse models, but *Nesprin1* KO mice have no overt phenotypes related to muscular dystrophy. By contrast *Lmna*^{−/−} and *Lmna*^{H222P/H222P} mice are well-established models of autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD) [71,72]. Furthermore, muscle biopsies from patients affected by autosomal recessive cerebellar ataxia Type I (ARCA1), a neurological pathology associated with nonsense mutations of *Nesprin1*, display significant mispositioning of synaptic nuclei. However, ARCA1 patients have no clinical, ultrastructural, or electrophysiological

phenotypes related to skeletal muscle [73]. Intriguingly Mejat and colleagues [70] proposed that muscular dystrophy phenotypes originate from structural defects in the neuromuscular junction (NMJ), detected in *Lmna*^{-/-} and *Lmna*^{H222P/H222P} mice. However NMJs appear structurally normal in Nesprin1 KO mice, and in skeletal muscle expressing a transgenic dominant-negative KASH domain (Table I) [59,74].

How can mutations in A-type lamins, but not LINC complexes, specifically affect NMJ ultrastructure? Recent studies in *Drosophila* suggest a promising new hypothesis (Figure 3, Box II). During NMJ development, Wingless (wg), released by presynaptic terminals, binds to and activates endocytosis of its receptor, DFrizzled-2, at postsynaptic membranes. The cytoplasmic domain of DFrizzled-2 (DFz2c) is then cleaved and imported into myonuclei [75], wherein DFz2c forms foci with both *LamC* (the *Drosophila* A-type lamin) and ribonucleoparticles (RNPs) that contain mRNAs encoding synaptic proteins [76]. In a pathway similar to herpesvirus nuclear egress (see Hennig and O'Hare, this issue) these RNPs transit via INM-derived vesicles that fuse with the ONM for delivery to the cytoplasm (Figure 3, Box II) [77,78]. These foci do not form if *LamC* is absent or mutated, and the resulting NMJs have morphological defects, disrupted synaptic arbors and altered synaptic transmission [76,79]. These phenotypes resemble the NMJ defects seen in *Lmna*^{-/-} and *Lmna*^{H222P/H222P} mice and in AD-EDMD patient biopsies [70]. These findings collectively suggest that pathological mutations in A-type lamins can interfere with RNP trafficking across the NE and thereby disrupt the translation of synaptic transcripts at the NMJ. Mutations in other NE proteins involved in RNP trafficking are also predicted to disrupt protein expression at neuronal or muscular synapses. The discovery of a luminal protein, AAA+-ATPase TorsinA, required for RNP envelopment in *Drosophila* [80] is likely the first of many new molecular insights into human dystonias, neurological disorders characterized by involuntary sustained muscle contractions [81–84].

Nesprin1 beyond the nuclear envelope

Many synaptic components are translated locally from polyadenylated mRNAs that are trafficked to synapses [85]. Surprisingly the nesprin ortholog MSP-300 was recently identified as the most abundant mRNA immunoprecipitated by Syncrip, a *Drosophila* ortholog of human HRNPQ1 involved in localized synaptic translation [86,87] (Figure 3, Box III). Accordingly, *Syp* null flies display a significant reduction of MSP-300 protein and myonuclear clustering defects similar to *msp-300* mutant flies and *Nesprin1* KO mice [59,60,86]. The biological significance of synapse-localized translation of MSP-300 remains uncertain. However, other studies also point to functional connections between Nesprin1, RNPs and synapses. For example Nesprin1 was first identified in mammals by virtue of its interaction with Musk, a muscle-specific receptor tyrosine kinase highly concentrated at NMJ postsynaptic membranes [88], and a KASH-domain-deleted allele, *msp-300*^{KASH}, affects glutamate receptor density at the NMJ [61]. Interestingly Syncrip/HRNPQ1 is highly expressed in neuronal dendrites where a Nesprin1 isoform (CPG2) has a key role in glutamate receptor endocytosis at postsynaptic membranes [89]. Finally p50^{Nesp1}, a novel Nesprin1 isoform, was discovered as a component of P-bodies necessary for RNA granule dynamics in cultured cells [90]. These findings indicate specific functional roles for

Nesprin1 isoforms outside the nucleus and expand the mechanisms by which Nesprin1 mutations may contribute to CNS and striated muscle pathologies [73,91–95].

Novel functions for Nesprin1 beyond the NE are also supported by variable phenotypes that result from different genetic strategies to inactivate *Nesprin1* in mice. In addition to the previously-discussed *Nesprin1* KO mice, which harbor a partial deletion of the last exon encoding the KASH domain [59], other mouse models have been generated via full deletion of this last exon (*Nesprin1*^{KASH}) or using a floxed version of exon-16 (*Nesprin1*⁻¹⁶) [96,97]. These mouse models all have clustered myonuclei. However, in striking contrast to *Nesprin1* KO mice, *Nesprin1*^{KASH} and *Nesprin1*⁻¹⁶ show severe perinatal lethality and surviving mice suffer acute growth retardation and reduced exercise capacity. Phenotypic differences related to partial vs complete deletion of the last exon of *Nesprin1* are puzzling, but may be explained as a consequence of alternative splicing of the penultimate exon [96,98–100]. This splicing substitutes 99 C-terminal residues of Nesprin1, including the KASH domain, with 11 residues and thereby produces Nesprin1 isoforms with no KASH domain (KASH-LESS) [100]. KASH-LESS isoforms would not be affected by the genetic strategy used to raise *Nesprin1* KO mice, whereas the strategies used to create the *Nesprin1*^{KASH} and *Nesprin1*⁻¹⁶ alleles would change their C-terminal region. Because this particular splicing is specific to mouse CNS tissues [100], the phenotypic differences between *Nesprin1* KO mice, on one hand, and *Nesprin1*^{KASH} and *Nesprin1*⁻¹⁶ mice, on the other hand, may be due to the functional inactivation of KASH-LESS isoforms of Nesprin1 in CNS tissues. Finally, Nesprin1 expression in the human brain appears limited to neurons [101]. These considerations taken together strongly suggest a role for Nesprin1 isoforms at synapses as a new hypothesis relevant to the mechanisms of a growing number of human pathologies associated with *Nesprin1* mutations [10].

Conclusion

The identification and characterization of LINC complexes was a breakthrough in understanding the molecular mechanisms of nuclear migration and anchorage during skeletal muscle and CNS development. This field is moving fast, exemplified by the discovery that IKNM does not require LINC complexes but instead involves the sequential recruitment of dynein-based complexes to specific NPC proteins [29]. Interestingly, LINC complexes become physiologically relevant to CNS development after neural progenitors exit the cell cycle, playing essential roles in centrosome-directed nuclear translocation within newborn cortical neurons.

Even though disease-causing mutations of several NE components lead to nuclear mispositioning in skeletal muscle, the clinical significance of this spectacular phenotype remains elusive. Evidence accumulated from AD-EDMD mouse models and more recently in *Drosophila* suggest a novel hypothesis whereby these mutations disrupt RNP trafficking across the NE. Because these RNPs encode key synaptic proteins that are locally translated at synapses, disease-causing mutations in NE proteins might therefore indirectly disrupt synaptic function.

Major new concepts about the mechanisms and physiological functions of NE proteins have emerged over the past two years. Because these new concepts originate mainly from studies of the *Drosophila* NMJ, further testing in mouse models is needed. Given the plethora of functional roles for the plethora of alternatively spliced isoforms encoded by *Nesprin1* at neuromuscular and neuronal synapses, finely-tuned genetic strategies will be needed to understand the molecular etiology of nuclear ‘envelopathy’ diseases [10,102].

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ABBREVIATIONS

AD-EDMD	Autosomal Dominant Emery-Dreifuss Muscular Dystrophy
ARCA1	Autosomal Recessive Cerebellar Ataxia Type I
DKO	Double Knockout
IKNM	Interkinetic Nuclear Migration
INM	Inner Nuclear Membrane
KASH	Klarsicht/Anc1/ Syne1 Homology
KO	Knockout
LINC	Linkers of the Nucleoskeleton to the Cytoskeleton
NE	Nuclear Envelope
NMJ	Neuromuscular Junction
ONM	Outer Nuclear Membrane
PNS	Perinuclear Space (e.g., NE lumen)
RNPs	Ribonucleoprotein Particles
RPCs	Retinal Progenitor Cells
SUN	Sad1/Unc84

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Figure 1.

Topological representation and domain composition of Nesprins 1, 2, 3 and 4, which are encoded by distinct genes, in the context of their interaction with SUN proteins and cytoskeletal components. Dashed arrows indicate direct SUN/KASH interactions. *INM*, inner nuclear membrane. *ONM*, outer nuclear membrane.

Figure 2.

Nuclear movements accompanying CNS development. (A) Depiction of interkinetic nuclear migration within neural precursor cells (blue nuclei). (B) Centrosome-mediated nuclear translocation within post-mitotic neurons (green nuclei) migrating towards their final laminar position. *NBL*, neuroblast layer. (C) Apical migration of cone photoreceptor nuclei during postnatal retinogenesis. *OS*, outer segment (phototransduction). *IS*, inner segment (ER, mitochondria). *ONL*, outer nuclear layer that contains photoreceptor nuclei. *P*, postnatal day. The boxed inset shows the displacement of endogenous Nesprins from NE to ER membranes upon transgenic expression of EGFP-KASH2 specifically targeted to differentiating cone photoreceptors.

Figure 3.

Role of NE components in skeletal muscle development. (Box I) Depiction of LINC complexes in the context of myonucleus anchorage at the neuromuscular junction. *AchRs*, Acetylcholine Receptors. *NPC*, nuclear pore complex. (Box II) A-type lamins form nuclear foci at sites where DFz2C and ribonucleoproteins (RNPs) are trafficked across the NE. (Box III) Depiction of local translation of MSP-300 (Nesprin1) and other mRNAs at the NMJ.

Table 1

Overview of phenotypes associated with mutations in LINC complex proteins and A-type lamins in mouse and *Drosophila* suggest that loss of NMJ integrity, rather than myonuclear positioning defects, correlates with disease state (see text for details). This table also emphasizes Sun1 and Nesprin2 are more important for nucleokinesis during CNS and retina development than Sun2 and Nesprin1. *NR*, not reported. *N/A*, not applicable.

Models	Genetic alteration	Viability	Myonuclei positioning/NMJ integrity	CNS lamination	Photoreceptor nuclei positioning	References
Mice	Nesprin1 KO	viable	AFFECTED/NORMAL	NORMAL	NORMAL	27, 29, 60
	Nesprin2 KO	viable	NORMAL/NORMAL	PARTIALLY AFFECTED	AFFECTED	27, 29, 60
	Nesprin1/2 DKO	perinatal lethality	AFFECTED/NORMAL	AFFECTED	N/A	27, 29, 60
	Nesprin1 KASH	Low survival rate, reduced locomotion	AFFECTED/NR	NR	NR	98
	Nesprin1 -16	Low survival rate, reduced locomotion	AFFECTED/NR	NR	NR	97
	Sun1 KO	viable	PARTIALLY AFFECTED/NORMAL	AFFECTED	AFFECTED	27, 29, 55, 68
	Sun2 KO	viable	PARTIALLY AFFECTED/NORMAL	NORMAL	NORMAL	27, 29, 68
	Sun1/2 DKO	perinatal lethality	AFFECTED/NORMAL	AFFECTED (embryonic)	AFFECTED (rescued)	27, 29, 68
	Lmna ^{-/-}	Death by 8 weeks, reduced locomotion	AFFECTED/AFFECTED	NR	NORMAL	55, 71, 72
	Lmna H222P/H222P	Death by 13 months, reduced locomotion	AFFECTED/AFFECTED	NR	NR	71, 73
Drosophila	transgenic KASH in muscle	viable	AFFECTED/NORMAL	N/A	N/A	60, 74
	transgenic KASH in retina	N/A	N/A	N/A	AFFECTED	55
	Syncrrip	NR	AFFECTED/normal density of glutamate receptor	NR	NR	87
	Msp-300	altered larval motility	AFFECTED/decreased density of glutamate receptor	NR	NORMAL	31, 61
	klar	altered larval motility	AFFECTED/NR	NR	AFFECTED	31, 61
	Torsin	NR	NR/AFFECTED	NR	NR	81
	LamC	NR	NR/AFFECTED	NR	NR	77