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UnLINCing the nuclear envelope: towards an understanding of the physiological significance of nuclear positioning

David Razafsky, **Shulun Zang**, and **Didier Hodzic**[1]

Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, 660 S. Euclid Ave, St. Louis, MO 63110, U.S.A

Abstract

Appropriate tissue morphogenesis strictly requires the developmental regulation of different types of nuclear movements. LINC (linker of nucleoskeleton and cytoskeleton) complexes are macromolecular scaffolds that span the nuclear envelope and physically connect the nuclear interior to different cytoskeletal elements and molecular motors, thereby playing essential roles in nucleokinesis. Recent studies dedicated to the *in vivo* disruption of LINC complexes not only confirmed their widespread role in nuclear dynamics, but also led to a vigorous regain of interest in the physiological relevance of nuclear positioning within cells and syncitia. In the present paper, we review the results of LINC complex disruption *in vivo* across different organisms and the potential implications of observed phenotypes in human diseases.

Keywords

interkinetic nuclear migration; linker of nucleoskeleton and cytoskeleton complex (LINC complex); nesprin; neuronal migration; nuclear positioning; SUN protein

LINC complexes

It has now been more than a decade since studies in *Drosophila* [1,2] and *Caenorhabditis elegans* [3] identified proteins belonging to what are now generally called LINC (linker of nucleoskeleton and cytoskeleton) complexes, a diverse assortment of macromolecular scaffolds that span the NE (nuclear envelope) and connect the nuclear interior to the cytoskeleton (Figure 1). In vertebrates, LINC complexes form through the interaction between two families of transmembrane proteins within the perinuclear space that separates the INM (inner nuclear membrane) from the ONM (outer nuclear membrane) of the NE (see [4,5] for recent reviews). As shown in Figure 1, one family corresponds to integral transmembrane SUN proteins (SUN1 and SUN2) that populate the INM. SUN protein nucleoplasmic regions interact directly with nuclear lamins [6,7]. A hallmark of SUN proteins is the evolutionarily conserved C-terminal SUN (Sad1/Unc84) domain made of ~150 C-terminal amino acids that protrudes into the perinuclear space. There, the SUN domain interacts with the KASH (*Klarsicht*/ANC-1/SYNE homology) domain, the evolutionarily conserved molecular signature of nesprins, the other family of LINC complex

[1]To whom correspondence should be addressed (hodzicd@vision.wustl.edu).

proteins that populate the ONM. In mammals, four genes encoding nesprin-1, -2, -3 and -4 have currently been identified [8]. They lead to the tissue- and development-specific synthesis of a plethora of KASH domain-containing proteins whose nucleoplasmic regions vary greatly in size (~40 kDa–1 MDa) and harbour a variable number of spectrin repeats known to provide interacting interfaces with the cytoskeleton [9,10]. Interactions between specific mammalian nesprins with various cytoskeletal networks and molecular motors have been delineated (Figure 1). The giant isoforms of nesprin-1 and -2 possess an N-terminal calponin homology region that binds directly to actin [11,12]. Nesprin-3 interacts with plectin, thereby connecting the nucleus to intermediate filaments [13,14]. Finally, connection of nesprins to molecular motors is illustrated by the interaction of nesprin-4, whose expression is restricted to secretory epithelia, with kinesin-1 [15] and of nesprin-1 and -2 with dynein complex components [16,17]. Early studies pointed to a central role for SUN proteins and nesprins in nuclear positioning. Indeed, mutations of either *Klarsicht* (KASH) or *Klaroid* (SUN) affect apical nuclear migration in developing *Drosophila* eye disc and mutations of *Unc84* (SUN), *Unc83* (KASH) or *Anc1* (KASH) in *C. elegans* alter nuclear migration and/or anchorage during hypodermal syncytium development [18]. In vertebrates, recent studies not only confirmed the essential role of LINC complexes in different aspects of nuclear positioning *in vivo*, but also emphasized the physiological importance of nuclear positioning at various developmental stages.

Nuclear positioning in skeletal muscle

Mouse models of LINC complex disruption have clearly shown that SUN proteins and nesprins govern nuclear anchorage in skeletal muscle [19–22]. Myonuclei are regularly spaced along muscle fibres, whereas groups of four to five closely juxtaposed nuclei, called synaptic nuclei, are anchored just beneath arrays of acetylcholine receptors at the neuromuscular junction. Genetic ablation of *Syne1*, which encodes nesprin-1 in mice, results in mispositioning of both synaptic and extrasynaptic nuclei in skeletal muscle fibres [19,21]. However, loss of function of *Syne2*, which encodes nesprin-2, does not affect myonuclei anchorage [19]. This is rather surprising, because nesprin-1 and -2 are both expressed in skeletal muscle [23] and display similar architectural organization. Because the nesprin-1-encoding gene encodes a wide array of isoforms originating from the combined use of multiple internal promoters and alternative splicing [10], the identity of nesprin-1 isoforms that are involved in synaptic nuclei anchorage remains to be established. The giant isoform of nesprin-1, because of its ability to directly connect the NE to the actin network through its N-terminal actin-binding domain, is an ideal candidate for such a task. However, shorter nesprin isoforms are predominantly expressed in adult skeletal muscle in comparison with their giant counterparts [23,24]. These results therefore suggest that shorter nesprin-1 isoforms may potentially play a significant role in myonuclear anchorage as well. Because desmin is also required for myonuclei positioning [25] and nesprins have the potential to interact with and recruit intermediate filaments at the nuclear periphery [13,14], one can envisage a mechanism where smaller isoforms of nesprins may interact with desmin to mediate myonuclear anchorage. Taken together, these data clearly indicate that LINC complexes govern myonuclei anchorage in skeletal muscle fibres. However, whether abnormal positioning of synaptic nuclei is associated with the molecular aetiology of

muscular dystrophies can be questioned, because there is a lack of correlation between myonuclei mispositioning and the development of muscular pathologies in different mouse models of nesprin-1 gene inactivation [19,21,26,27]. Furthermore, mutations of nesprin-1 associated with autosomal recessive cerebellar ataxia alter synaptic nuclei positioning [28], even though affected patients do not show any overt clinical manifestation of muscular dystrophy. Hence, it seems that new hypotheses need to be invoked in order to account for the reported mutations of nesprin-1 and -2 in muscle and cardiac pathologies [29,30]. In that respect, several lines of evidence point to KASH-less isoforms of nesprins. First, the use of KASH-less isoforms is not uncommon in *C. elegans* and *Drosophila* [18]. For example, the alternative splicing of the KASH domain of *Klarsicht* in *Drosophila* embryos redirects KASH-less isoform to lipid droplets rather than the NE [31]. Secondly, bioinformatic analyses strongly suggest the evolutionary conservation of the skipping of nesprin-1 penultimate exon that leads to KASH-less isoform synthesis in vertebrates and nesprin-1 and -2 transcripts that putatively encode KASH-less isoforms have been reported [10,21,24]. Thirdly, nesprin-2 immunoreactivity has been reported in Z-lines and sarcoplasmic reticulum of skeletal muscle [24] as well as at filipodia and microspikes [32]. These results, in addition to the property of spectrins to bind multiple cytoskeletal elements, therefore suggest that KASH-less nesprins may play important structural roles away from the NE that may also be impaired by mutations associated with cardiac or skeletal muscle pathologies. Examining these hypotheses will require both the identification of additional pedigrees to clearly establish the causality of reported nesprin mutations in skeletal muscle and cardiac pathologies and the sustained development of appropriate antibodies to unequivocally identify the complex pattern of nesprin isoforms synthesis in different tissues and cell types.

Nuclear positioning in the CNS (central nervous system)

CNS development is accompanied by a spectacular array of nuclear movements that are illustrated throughout the development of the retina, an accessible extension of the CNS (Figure 2).

The first of these movements, called IKNM (interkinetic nuclear migration), consists of oscillations of neuroblast nuclei between the apical and basal side of pseudostratified neuroepithelia (Figure 2, I). Remarkably, these nuclear movements are coupled to the cell cycle in that mitoses take place on the apical side while S-phase takes place at more basal locations. By opposition to neuronal migration (see below), nuclear movements during IKNM are not associated with any movement of the centrosome, which remains at the apical side of neuroepithelial cells. IKNM requires kinesins, dynein–dynactin complexes and actomyosin [33–35]. Importantly, interfering with cell-cycle progression blocks IKNM, whereas interfering with IKNM does not prevent cell-cycle progression. In the latter case, however, nuclear mispositioning during IKNM compromises the timing of neurogenesis [36]. For example, zebrafish strains carrying dynactin mutations display defective IKNM that result in larger and smaller populations of early-born and later-born neurons respectively [34]. Interestingly, down-regulation of the zebrafish nesprin-2 homologue also leads to an increased number of early-born neurons and a significant decrease in later-born neurons [34]. In agreement with a role of LINC complexes during IKNM, both nesprin-2$^{-/-}$ and *Sun1*/*Sun2* DKO (double-knockout) mouse brain and retina tissues display ectopic mitotic

and S-phase nuclei, indicating IKNM defects [16,17]. Furthermore, the early depletion of neural progenitors observed in nesprin-2$^{-/-}$ and *Sun1*/*Sun2* DKO mouse brain also suggest an imbalance between differentiation and proliferation of neural precursors. These results, in conjunction with the evolutionarily conserved interaction between nesprins and molecular motors [15–17,37,38], strongly suggest that LINC complexes are indispensable to recruit molecular motors at the NE to sustain nuclear translocation during IKNM.

Upon exit from the cell cycle (Figure 2, II), post-mitotic neurons migrate from the apical side of the neuroblast layer towards their final laminar position [39]. It is now well established that neuronal migration is tightly coupled to nuclear translocation. Nuclear translocation consists of the forward saltatory movement of the nucleus behind the centrosome that moves at a relatively constant velocity. The physical coupling of the centrosome to the nucleus during nuclear translocation is absolutely essential [39–43]. A variety of human syndromes associated with the failure of radial neuronal migration and the ensuing abnormal lamination of the cerebral cortex is associated with the mutation of *LIS1* and *DCX* [44–46]. These mutations severely impair centrosome coupling to the nucleus during nuclear translocation. Similarly, *Sun1*/*Sun2* DKO and nesprin-2$^{-/-}$ mice display major disconnections between nuclei and centrosomes that result in failure of radial neuronal migration in the cerebral cortex [16]. Curiously, nesprin-2 alone is strictly required for radial neuronal migration within developing cortex and hippocampus, whereas it acts redundantly with nesprin-1 in cerebellum, midbrain and hindbrain [16]. Whether these observations reflect tissue-specific expression or tissue-specific function of either nesprin-1 or -2 isoforms remains to be established. The same question also arises for *Klaroid* (SUN) and *Klarsicht* (KASH) whose mutations solely affect eye development in *Drosophila* [38]. Alteration of the nuclear lamina also affects neuronal migration. Mutations of *Lam Dm*(*0*), which encodes a B-type lamin in *Drosophila*, phenocopy the same migration defect than *Klaroid* (SUN) and *Klarsicht* (KASH) mutants, suggesting that the nuclear lamina also plays essential role in neuronal migration [47]. Accordingly, Coffinier et al. [48,49] recently demonstrated that lamin B2$^{-/-}$ mice display profound lamination failures of the cerebral cortex and cerebellum owing to impaired neuronal migration. The lamin–SUN–nesprin ‘axis’ is therefore essential to neuronal migration.

Finally, within the adult retina (and the CNS in general), the positioning of nuclei from different cell types at very precise spatial locations is a striking, but poorly studied, phenomenon (Figure 2, III). For example, cone nuclei are strictly localized at the apical side of the ONL (outer nuclear layer) and Müller cells, whose cell bodies extend across the whole retina, invariably position their nuclei in the middle of the INL (inner nuclear layer). One can wonder how and why these cells position their nuclei at such specific locations. In zebrafish, either the forced expression of dominant-negative polypeptides or morpholino approaches targeting *Lis1*, the dynactin complex or LINC complexes in fully differentiated retina displace photoreceptor nuclei to basal locations [50]. A similar phenotype consisting of a more basal location of cone photoreceptor nuclei is also observed in retinas from *Sun1*$^{-/-}$ mice [17]. These results suggest that nuclear positioning in fully differentiated neurons is an active process that involves the same families of proteins that translocate the nucleus during neurogenesis. Finally, the impaired viability of zebrafish photoreceptors with mispositioned nuclei emphasizes the physiological requirement of LINC complexes in fully

differentiated neurons. To that respect, it is interesting to note that the perinatal lethality of *Sun1*/*Sun2* DKO mice could be partially rescued by the transgenic expression of Sun1 driven by a neuron-specific enolase promoter [22].

Concluding remarks

Taken together, these data clearly show that nuclear lamina connections to molecular motors via LINC complexes provide for evolutionarily conserved ‘nuts and bolts’ that are essential to neurogenesis, neuronal migration and CNS morphogenesis. To our knowledge, only one study directly associates mutations of LINC complex components with neurological disorders. Indeed, mutations of nesprin-1 have been reported in ARCA1 (autosomal recessive cerebellar ataxia 1) that involves the progressive development of locomotor abnormalities developing at early to mid-adulthood [28]. Given the recent progress in our understanding of the physiological functions of LINC complexes during CNS development and maintenance, ARCA1 mutations probably represent the tip of the iceberg regarding the involvement of LINC complex components in human neurological pathologies.

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Abbreviations used

ARCA1	autosomal recessive cerebellar ataxia 1
CNS	central nervous system
DKO	double-knockout
IKNM	interkinetic nuclear migration
INM	inner nuclear membrane
KASH	*Klarsicht*/ANC-1/SYNE homology
LINC	linker of nucleoskeleton and cytoskeleton
NE	nuclear envelope
ONM	outer nuclear membrane

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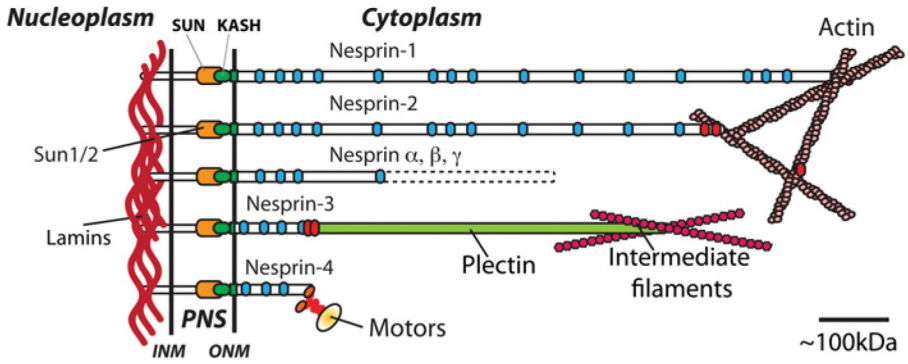

Figure 1. Interactions of SUN proteins and nesprins

Depiction of SUN proteins and nesprins whose interactions through evolutionarily conserved SUN and KASH domains provide macromolecular scaffolds that span the NE and mediate physical interactions between cytoplasmic and nucleoplasmic components (see the text for more details). Blue ovals are spectrin repeats; red ovals are actin-binding domains. PNS, perinuclear space.

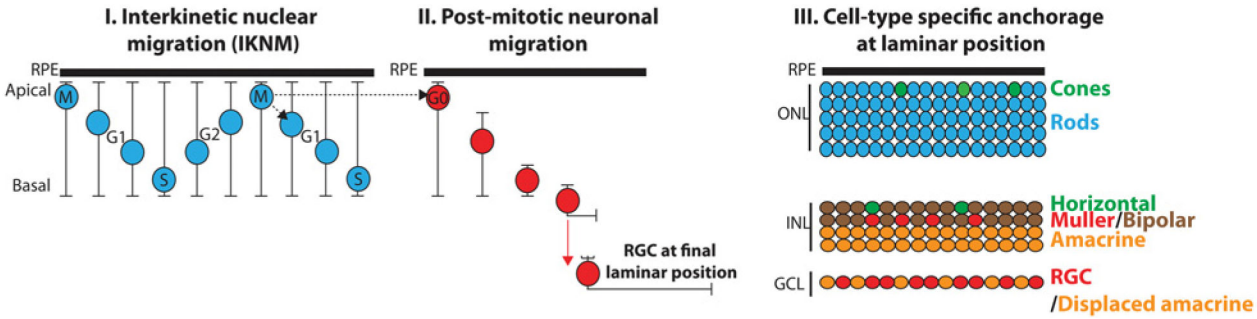

Figure 2. Depiction of nuclear movements associated with retinal development, an integral part of the CNS

See the text for details. GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; RGC, retinal ganglion cells, the first cells to exit the cell cycle in the developing retina; RPE, retinal pigment epithelium.