



REVIEW

Chain reaction: LINC complexes and nuclear positioning

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Abstract

Nuclear positioning plays an essential role in defining cell architecture and behaviour in both development and disease, and nuclear location frequently adjusts according to internal and external cues. For instance, during periods of migration in many cell types, the nucleus may be actively repositioned behind the microtubule-organising centre. Nuclear movement, for the most part, is dependent upon coupling of the cytoskeleton to the nuclear periphery. This is accomplished largely through SUN and KASH domain proteins, which together assemble to form LINC (linker of the nucleoskeleton and cytoskeleton) complexes spanning the nuclear envelope. SUN proteins of the inner nuclear membrane provide a connection to nuclear structures while acting as a tether for outer nuclear membrane KASH proteins. The latter contain binding sites for diverse cytoskeletal components. Recent publications highlight new aspects of LINC complex regulation revealing that the interplay between SUN and KASH partners can strongly influence how the nucleus functionally engages with different branches of the cytoskeleton.

Keywords

Nucleus, Nuclear positioning, Nuclear envelope, LINC complex, SUN domain, KASH domain, Nesprin, Cytoskeleton

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Introduction

The defining feature of metazoa is recruitment of diverse cell types into a broad range of tissues and organ systems. Such specialisation during development goes hand-in-hand with oftentimes extensive cellular remodelling. Think of non-contractile myoblasts fusing to form mature muscle fibres or neuroepithelial cells transforming into cortical neurons. Reorganisation of cellular architecture almost invariably involves structural and compositional changes to the cytoskeleton, repositioning of organelles, and expansion or contraction of different cellular compartments. Even the nucleus, as the largest organelle in multicellular animals, may be the object of large-scale movements¹. In certain cell types such as erythroblasts, it is even dispensed with entirely in a process of active ejection.

What has become increasingly clear is that the nucleus maintains extensive contacts with the cytoskeleton. In this way, it may function as a nexus for the dissemination of mechanical forces throughout the cell. It is also apparent that nuclear components may experience physical forces originating in the cytoplasm or even in the extracellular environment. This was demonstrated by Maniotis *et al.*, who used ligand-coated beads to displace extracellular matrix-associated plasma membrane proteins and their coupled cytoskeletal elements². The result was distortion and dislocation of intracellular structures, including the nucleus, in the direction of bead movement. More surprising was the corresponding displacement of intranuclear landmarks such as nucleoli. Related experiments in which a microneedle was used to directly perturb cytoplasmic structures, including the cytoskeleton, gave qualitatively similar results. These conceptually simple experiments implied that there must be structures at the nuclear envelope (NE) that can mechanically couple nuclear and cytoplasmic components³. The identification of such structures in the intervening years has represented an important advance in our understanding of the biology of the NE and how this contributes to the organisation of both the nucleus and the cytoplasm⁴⁻⁷.

LINCing the nucleus and cytoskeleton

The interface between nuclear and cytoplasmic compartments is formed by the NE⁸. Its most prominent features are inner and outer nuclear membranes (INM and ONM) separated by a perinuclear space (PNS). The ONM shares multiple connections with the endoplasmic reticulum to which it is functionally related. In contrast, the INM contains a unique array of integral membrane proteins that associate with nuclear components. Despite compositional differences, the INM and ONM display continuities at sites occupied by nuclear pore complexes (NPCs), massive channels that mediate movement of macromolecules back and forth across the NE. The final significant component of the NE is the nuclear lamina, a filamentous meshwork composed of A- and B-type lamins which is associated with the nuclear face of the INM and which provides structural integrity to the NE^{9,10}.

Molecular details of force transmission between the nucleus and cytoplasm first emerged from observations that cytoplasmic dynein was recruited to the NE during G₂ of the cell cycle¹¹⁻¹³. This was subsequently shown to facilitate NE breakdown and dispersal during mitotic prometaphase^{14,15}. In essence, NE-associated

dynein, engaging with astral microtubules, serves to peel open the NE. However, it is obvious that, to be effective, a dynein anchor at the nuclear surface must be able to transmit forces across the nuclear membranes to the nuclear lamina. Ensuing studies implicated NPCs as just such an anchor, and two distinct NPC-associated dynein-binding sites were identified. The first of these involved the Nup107/160 complex, which is a major component of the structural framework of the NPC¹⁶. The second dynein-binding site featured Nup358/RanBP2, a component of filament structures that extend from the NPC framework into the cytoplasm¹⁷. In addition to NE breakdown, NPC-associated dynein is required to drive vectorial nuclear movement in certain cell types. A notable example is interkinetic nuclear migration (IKNM) in neuroepithelial cells¹⁶. One aspect of IKNM is dynein-mediated basal-to-apical movement of nuclei during G₂ of the cell cycle. This occurs as a prelude to cell division and is essential for ordered development of the central nervous system.

The role of NPCs as cytoskeletal attachment sites is restricted to the microtubule system and then only for limited periods during the cell cycle. During interphase in most somatic cells, it is LINC (linker of the nucleoskeleton and cytoskeleton) complexes that sustain this function^{1,6}. LINC complexes are versatile structures recognised in all nucleated cells examined to date. This includes plant^{18,19} and animal²⁰⁻²³ as well as fungal²⁴⁻²⁶ cells. LINC complexes are assembled from members of two families of integral membrane proteins. SUN (Sad1, UNC-84) domain proteins are residents of the INM in which their N-terminal regions are exposed to the nuclear contents while C-terminal sequences, consisting of a coiled-coil region that terminates in the eponymous, roughly 200-residue SUN domain, extends into the PNS. In mammals, there are five genes encoding orthodox SUN proteins²⁷. However, only two of these, *SUN1* and *SUN2*, are widely expressed.

SUN proteins typically function as transluminal tethers for ONM KASH (Klarsicht, ANC-1, SYNE, Homology) domain proteins⁴. All members of the KASH family engage directly with available SUN domains through a short, roughly 30-residue, C-terminal sequence exposed to the PNS. The cytoplasmic N-terminal region of KASH family members binds components of the cytoskeleton. In this way, LINC complexes, spanning both nuclear membranes, are able to mechanically couple nuclear and cytoplasmic structures.

SUN proteins are clearly of ancient origin given their presence in all eukaryotic groups, where they have broadly similar roles. Indeed, glycosylated SUN homologues have even been recognised in archaeal cell walls. Based partly on such findings, Baum and Baum have suggested an intriguing “inside-out” model for the acquisition of nuclei and other membrane-bound compartments in eukaryotic cells²⁸. They propose that SUN proteins, and later LINC complexes, made a significant contribution to this key evolutionary process.

LINC diversity

The role of LINC complexes in nuclear positioning and anchoring was first recognised in *Caenorhabditis elegans* by Starr and Han^{29,30}. They showed that a large actin-binding protein, ANC-1,

a prototypic KASH family member, was required for tethering hypodermal cell nuclei. Localisation of ANC-1 to the ONM was found to be dependent upon the SUN protein UNC-84. The single *C. elegans* lamin (lamin C) in turn was found to be essential for UNC-84 localisation³¹. The inference was that UNC-84 together with ANC-1 formed a protein bridge that crossed the NE and that coupled the nuclear lamina to actin filaments. Similar SUN–KASH protein pairs had also been identified in both budding and fission yeast where they were shown to have roles in spindle pole assembly and organisation as well as in meiotic chromosome dynamics^{24,25,32,33}. In *Drosophila*, LINC complexes consisting of the SUN protein Klaroid and the dynein-binding KASH protein Klarsicht were found to be essential for IKNM in the developing eye^{34,35}. Other *Drosophila* LINC components contribute to muscle organisation^{36–39}. Even in plants, nuclear positioning and movement are mediated by LINC complexes, featuring SUN family members that engage with functional homologues of fungal and animal KASH proteins^{40–43}.

In mammals, there are six KASH proteins, of which five have well-characterised LINC complex functions^{4,6,44}. Two of these, Nesprin1 (Nesp1) and Nesprin2 (Nesp2), are encoded by a pair of complex genes featuring more than 100 exons⁴⁵. The largest isoforms of Nesp1 and 2, Nesprin1-Giant and Nesprin2-Giant (Nesp1G and Nesp2G), have masses of about 1 MDa and 800 kDa, respectively. Like ANC-1, each bears an N-terminal actin-binding site consisting of paired calponin-homology domains. In the case of at least Nesp2G, actin association is enhanced by an interaction with the actin nucleating protein formin, FHOD1, as well as with fascin, an actin bundling protein^{46,47}. Both Nesp1 and 2 also contain binding sites for kinesin-1 and cytoplasmic dynein. In this way, Nesp1 and Nesp2, depending upon the isoform, can associate with the actin or microtubule systems or both. In developing muscle cells, Nesp1 is involved in the recruitment of centrosomal proteins to the NE, thereby co-opting the nucleus as a new microtubule-organising centre (MTOC)^{48,49}. Similarly, a recent report⁵⁰ describes an association between Nesp1 and rootletin, a filament protein that forms ciliary rootlets. The implication is that Nesp1 may have a role in ciliary anchoring in a variety of cell types, including photoreceptors.

The third member of the family, Nesp3, binds plectin, a cytolinker molecule that provides a connection between the NE and the intermediate filament system⁵¹. Nesp4 and KASH5 function as NE adaptors for kinesin-1 and cytoplasmic dynein, respectively^{52,53}. Nesp4 is required for nuclear positioning in certain epithelial cells and is essential for viability of outer hair cells of the inner ear⁵⁴. Accordingly, Nesp4 mutations are linked to early-onset hearing loss⁵⁴. KASH5 is expressed primarily in meiotic cells and is responsible for telomere-led chromosome movements that culminate in homologous chromosome pairing⁵³. In *C. elegans*, ZYG-12, a dynein-binding KASH protein⁵⁵, has an analogous role^{56,57}, while in budding and fission yeast, Kms1 and Csm4 perform roughly equivalent meiotic functions^{33,58,59}.

LINC adjustments

Given the operational diversity of KASH proteins, it would seem logical that it is these that uniquely define LINC complex

specificity. This view is reinforced by findings that mice deficient in either SUN1 or SUN2 are viable, indicating that these proteins, both widely (albeit not exclusively) co-expressed, are functionally redundant⁶⁰. However, recent articles have thrown a cat amongst this particular flock of pigeons. Gomes *et al.* have focused on the role of Nesp2G in nuclear repositioning during cell migration⁶¹. It is well established that in migrating mouse 3T3 cells the MTOC becomes oriented towards the cell leading edge in front of the nucleus⁶¹. However, the MTOC itself remains stationary at the cell centroid and instead it is the nucleus that actually moves rearward. This was demonstrated in classic scratch-wound assays on 3T3 monolayers. Although rearward movement occurs relative to the MTOC, the process itself is driven not by microtubules but rather by the retrograde flow of dorsal actin filaments that engage with LINC complexes in the NE. A consequence of this interaction is recruitment of Nesp2G, SUN2 and lamins into TAN (transmembrane actin-associated nuclear) lines subjacent to the actin filaments^{62,63}. An additional ONM protein, Samp1 (NET5), also localised to TAN lines, is thought to contribute to the SUN2–lamin association⁶⁴.

To explore nuclear reorientation, Zhu *et al.*⁶⁵ devised a clever yet simple method. Employing the same scratch wound-type assay on cells grown on coverslips, nuclei were displaced by centrifugation. This was carried out by orienting the centrifugal field parallel to the coverslip surface and at right angles to the scratch in the cell monolayer. In this way, nuclei were moved to the front of cells on one side of the scratch while, on the other side, nuclei were displaced to the rear. The authors then followed the recovery of nuclei to their equilibrium positions. These experiments revealed that when the nucleus was displaced forwards it was returned to its correct location behind the MTOC in an actin- and myosin-dependent manner. This required LINC complexes containing Nesp2G and SUN2 and featured TAN line formation. However, when the nucleus was displaced rearwards, recovery was found to be dependent not on actin but on the microtubule system. In this case, nuclear movement was driven by cytoplasmic dynein. The identity of the dynein adaptor at the ONM was none other than Nesp2G. Evidently, cytoskeletal associations of Nesp2G may be modulated on the basis of the directionality of nuclear movement. However, the biggest surprise here was that for anterograde microtubule-dependent nuclear recovery, the LINC complex partner for Nesp2G was not SUN2 but rather SUN1. In the absence of SUN1, anterograde recovery was eliminated. The implication here is that the LINC complex partner of Nesp2G, either SUN1 or SUN2, is dictated by (or determines) the nature of its association with the cytoskeleton. The role of SUN proteins in either defining or reflecting the cytoskeletal engagement of Nesp2G is reinforced by the finding that the two SUN proteins can exert transdominant effects. Overexpression of SUN2 biases Nesp2G towards the actin system whereas overexpression of SUN1 has the reverse effect. The mechanisms underlying the differential effects of SUN1 versus SUN2 on the cytoskeletal interactions of Nesp2G are far from clear. However, they must in some way reflect the nature of the forces applied by actin versus microtubule systems and how they are accommodated by the two SUN proteins. Recent work from Cain *et al.*⁶⁶ also points to mechanistic differences in the way that LINC complexes may transmit sustained forces generated

by the actin cytoskeleton versus transient forces generated by the microtubule system.

Something new under the SUN

The original structural analyses of SUN–KASH complexes revealed that SUN2 SUN domains are organised as homotrimers^{67,68}. *In vivo* this would involve the association of three SUN2 monomers by the formation of an extended triple-helical coiled coil that links the SUN2 transmembrane sequences to the terminal SUN domains. Association with a Nesp1 or Nesp2 KASH domain occurs mainly at contact sites between SUN domains within each trimer. This interface is formed where an anti-parallel beta-structure (the “KASH-lid”) extending from one SUN domain overlaps with the core structure of its neighbor. LINC complex assembly involves 18 to 23 amino acids at the KASH domain C-terminus. These are organised in an extended conformation and are accommodated largely within a groove beneath the KASH-lid. However, the four terminal amino acids of the KASH domain, comprising a PPPX (P is proline and X is any amino acid) motif, fit into a discrete pocket within a single SUN monomer. Integrity of this motif is crucial for the SUN–KASH interaction. Extension of this sequence by only a single alanine abolishes association. The implication is that the SUN–KASH interaction is initiated by the PPPX tetrapeptide followed by “zippering-up” of the KASH sequence within the binding groove. Additional KASH residues are also important: a tyrosine at position -7 (Y(-)7) and a cysteine at position -23. The latter is able to form a disulphide bond with a conserved cysteine residue (C563 in human SUN2) within the SUN domain. Cain *et al.* examined the role of these different KASH residues in *C. elegans* LINC complexes *in vivo*⁶⁶. In particular, they explored interactions of the SUN protein UNC-84 with its two partners: ANC-1 and UNC-83. The latter is a KASH protein that binds kinesin-1 and cytoplasmic dynein and is required for nuclear migration in hypodermal precursor cells^{69–71}. As we have seen, ANC-1 is required for actin-dependent nuclear anchoring in the hypodermis²⁹. For both ANC-1 and UNC-83, integrity of the C-terminus is paramount for productive association with UNC-84. The Y(-)7 in UNC-83 also proves to be essential. While still localising to the NE, an alanine substitution at this position renders UNC-83 incapable of supporting nuclear migration. The inference is that interaction with UNC-84 is sufficiently weakened so that it cannot withstand application of forces encountered during kinesin-driven nuclear movement. In contrast, disulphide bond formation is not required. Indeed, UNC-83 has a foreshortened KASH domain that lacks the key cysteine residue. The reverse is found to be true for ANC-1. Y(-)7 is dispensable, while the cysteine at -23 is absolutely required for nuclear anchoring. The suggestion is that for short-term processes such as UNC-83 and microtubule-driven migration, maintenance of SUN–KASH interactions by a disulphide bond may be unnecessary. By contrast, long-term anchoring via actin may require disulphide-dependent LINC complex stabilisation. This notion makes some sense since the mammalian dynein-binding KASH protein KASH5, which has only a transient function in meiotic cells, like UNC-83 has a foreshortened KASH domain and lacks the cysteine at -23. The role of disulphide bond

formation in the stabilisation of SUN2–Nesp2 association is brought further into focus in molecular dynamics studies⁶⁶. Loss of this bond results in significantly weakened interactions, and application of pulling forces to the Nesp2 KASH peptide causes its partial detachment. Moreover, both the KASH peptide and the SUN2 KASH-lid become stretched out to accommodate the applied forces. With the disulphide bond intact, however, forces are transmitted beyond the SUN–KASH interface and instead are relieved by stretching of the triple-helical coiled coil.

It is obvious that diverse KASH proteins display subtly different associations with their cognate SUN proteins. However, this cannot easily explain observations that the cytoskeletal interactions of Nesp2 are reflected in its discrimination between SUN1 and SUN2⁶⁵. It seems likely, however, that the key to this puzzle lies in how forces across LINC complexes are dissipated. Studies by Nie *et al.* and Xu *et al.* suggest that the triple-helical coiled coil may play a significant role in the regulation of SUN–KASH interactions^{72,73}. Structural analyses reveal that the luminal coiled-coil domain is actually formed from two separate helical segments, CC1 and CC2, which are connected by a flexible linker. By the same token, CC2, which lies closest to the SUN domain, is itself formed from three shorter helices. These helices, in addition to facilitating trimerisation of SUN2 monomers, can adopt an alternative structure in which they form an intra-chain triple-helical bundle. In this conformation, CC2 is able to associate with the SUN domain KASH-lid, thereby effectively blocking LINC complex formation. In this way, CC2 functions as an auto-inhibitory domain (AID). Clearly, CC2 must be able to switch reversibly between its inhibitory conformation and its extended conformation permissive for trimerisation and KASH binding. What is not clear is whether this switching may still occur after trimer formation⁷⁴. If it can occur, then it opens up a range of regulatory possibilities. In one such model, tension applied to CC2 via a bound KASH domain should favour its extended permissive conformation over its inhibitory conformation. Given that there is some divergence between SUN1 and SUN2 CC2/AID sequences, it is possible that one or the other may be more prone to switching to the AID conformation. Certainly, Hennen *et al.*⁷⁵ and Jahed *et al.*⁷⁶ have documented differences in the limitations of SUN1 versus SUN2 homo-oligomerisation. As an example, the actin system may be less effective at retaining SUN1 in its permissive conformation when compared with the microtubule system. Thus, Nesp2G, when bound to actin, may be biased away from SUN1. Conversely, Nesp2G, when engaged with kinesin-1, may be biased towards SUN1 because of its ability to prevent auto-inhibition by CC2. This model would be consistent with observations that in mammalian systems, all microtubule-associated LINC complexes seem to be based around SUN1, regardless of whether they contain Nesp2, Nesp4 or KASH5. It is also certain that additional factors, such as the AAA⁺ (ATPase associated with various cellular activities) protein TorsinA, contribute to these various SUN–KASH associations⁷⁷. Intriguingly, a recent report described a *Drosophila* ONM protein, Kuduk (Kud), which associates either directly or indirectly with KASH proteins⁷⁸. Kud appears to suppress NE anchorage of KASH proteins lacking

cytoskeletal interactions. In this way, Kud and its mammalian homologue TMEM258 may function as a quality control or chaperone for the assembly of LINC complexes that are engaged with the cytoskeleton.

The scheme outlined here, which involves SUN auto-inhibition and which draws on work from several laboratories, cannot be the whole story. The model, as it stands, cannot easily explain reciprocal transdominant effects of SUN1 versus SUN2 in Nesp2G-dependent nuclear positioning⁶⁵. However, taken together, all of these recent biophysical and cell biological studies have hinted at previously unappreciated levels of LINC complex

adaptation. There is no question that these may impact diverse aspects of cell function from mechanotransduction to migration and will open new avenues of research activities.

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