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Connecting the nucleus to the cytoskeleton by SUN–KASH bridges across the nuclear envelope

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The nuclear–cytoskeleton connection influences many aspects of cellular architecture, including nuclear positioning, the stiffness of the global cytoskeleton, and mechanotransduction. Central to all of these processes is the assembly and function of conserved SUN–KASH bridges, or LINC complexes, that span the nuclear envelope. Recent studies provide details of the higher order assembly and targeting of SUN proteins to the inner nuclear membrane. Structural studies characterize SUN–KASH interactions that form the central link of the nuclear-envelope bridge. KASH proteins at the outer nuclear membrane link the nuclear envelope to the cytoskeleton where forces are generated to move nuclei. Significantly, SUN proteins were recently shown to contribute to the progression of laminopathies.

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Introduction

How the nucleus interacts with the cytoskeleton is central to positioning the nucleus, which functions in a wide variety of cellular processes including nuclear migration, nuclear anchorage, centrosome attachment to the nucleus, and mechanotransduction [1–4]. The machinery that positions nuclei also plays important functions in DNA repair and pairing of chromosomes in meiosis, which will not be discussed here [5–10]. A conserved bridge consisting of SUN and KASH proteins spans both membranes of the nuclear envelope [11–13] and is often referred to as the LINC complex because it is the linker of the nucleoskeleton to the cytoskeleton [14,15,16••]. To form the bridge, SUN proteins in the inner nuclear membrane interact with lamins in the nucleoplasm and KASH proteins in the perinuclear space (Figure 1). KASH proteins are then recruited specifically to the outer nuclear membrane where they are positioned to interact with a wide variety of cytoskeletal components [11]. Mutations in mammalian SUN and KASH proteins lead to developmental defects in neurogenesis, gametogenesis, myogenesis, cilliogenesis, and retina formation and contribute to human diseases, including muscular dystrophy, ataxia, Progeria, lissencephaly, and cancer [11,17,18,19,20••].

The rapidly growing field of nuclear–cytoskeletal interactions has recently been reviewed [11–13]. Here, with apologies to the rest of the field, we focus on five major findings reported over the past two years. The first step of building the SUN–KASH bridge is recruiting SUN proteins to the inner nuclear membrane. Surprisingly, trafficking SUN proteins to the inner nuclear membrane involves multiple, partially redundant mechanisms [21•,22••,23••]. The second step of bridge building, the formation of a physical interaction between SUN and KASH domains, was recently beautifully elucidated at a structural level [16••]. Once KASH proteins are recruited to the surface of the nucleus, they interact with microtubule motors or flowing actin filaments to move nuclei [24,25,26••,27••]. A fourth group of studies demonstrated that SUN–KASH bridges transfer forces across the nuclear envelope [3,28•]. Finally, our understanding of the role of SUN proteins in disease has been advanced with the surprising finding that the absence of Sun1 suppresses disease pathologies associated with defects in lamin A [20••]. These exciting studies not only advance our understanding of how SUN–KASH bridges are assembled and function, but also open exciting avenues for continued research.

Building SUN–KASH bridges 1: targeting SUN proteins to the inner nuclear membrane

To assemble the bridge, SUN proteins must first be targeted specifically to the inner nuclear membrane. Upwards of 100 proteins are specifically targeted to the inner nuclear membrane using a variety of different mechanisms [29]. Here we focus on recent reports elucidating mechanisms used to target SUN proteins, specifically mammalian Sun1 and Sun2, *Caenorhabditis elegans* UNC-84, and *Saccharomyces cerevisiae* Mps3 to the inner nuclear membrane [21•,22••,23••,30•]. These reports show that SUN proteins are first actively trafficked from the ER to the nuclear envelope and then shuttled across nuclear pores by multiple mechanisms. Finally, SUN proteins are retained at the inner nuclear membrane through interactions with the nuclear lamina, chromatin, and/or KASH proteins (Figure 2).

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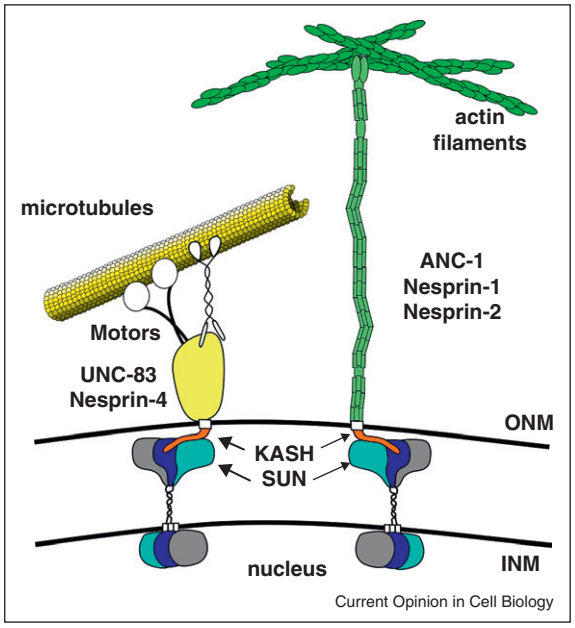
Figure 1



SUN and KASH proteins span the nuclear envelope. A trimer of SUN proteins (light blue, dark blue, and gray) forms at the inner nuclear membrane (INM). SUN proteins interact with the KASH domain (orange) in the perinuclear space. Only a single KASH protein is shown for simplicity. KASH proteins cross the outer nuclear membrane (ONM) and extend into the cytoplasm to interact with the cytoskeleton. One class of KASH proteins (yellow) recruit microtubule motors dynein and kinesin to the surface of the nucleus, while a second class (light green) tethers nuclei to actin filaments.

The first step of trafficking to the inner nuclear membrane is to actively move SUN proteins from the peripheral ER toward the nuclear envelope, which employs a variable combination of signals (Figure 2). Both Sun2 and UNC-84 contain a predicted inner nuclear membrane-sorting motif (INM-SM). INM-SMs are found next to the cytoplasmic end of a transmembrane span and bind a truncated, membrane-associated importin α during translation to facilitate transport toward the nuclear envelope [31,32]. A novel SUN-Nuclear Envelope Localization Signal (SUN-NELS) is conserved between UNC-84 and Sun1; SUN-NELS binding partners have not been identified [22••]. Mutating the INM-SM or the SUN-NELS in UNC-84 caused a significant delay in targeting to the nuclear envelope [22••]. Likewise, a short region containing the SUN-NELS in Sun1 participates in localization [33••]. An additional player in SUN trafficking is ATP, as depletion of ATP disrupted the mobility of Sun2 in the ER [30•]. Finally, a Golgi retrieval signal further ensures that SUN proteins get to the correct compartment. Mutating the Golgi retrieval signal in Sun2 caused it to mislocalize [23••]. Together, these data suggest that multiple mechanisms are required for presorting and trafficking SUN proteins toward the nuclear envelope. These signals likely work together, as multiple mutations worsened the trafficking defects [22••,23••].

Once enriched at the nuclear envelope, multiple mechanisms mediate the translocation of SUN proteins across the nuclear pore (Figure 2). The classical nuclear localization signal (cNLS) in Sun2 binds importins in a Ran-dependent manner and contributes to Sun2 localization [23••]. ATP may also play a role in translocation across the nuclear pore [30•]. The putative cNLSs in UNC-84 function in part redundantly with the SUN-NELS and INM-SM; only when all three signals are mutated does UNC-84 completely fail to localize to the inner nuclear membrane [22••]. Independently of cNLSs, Mps3 uses its N-terminal acidic domain to interact with the histone variant H2A.Z to transverse the nuclear pore complex [21•].

The final step of targeting SUN proteins is to retain them at the inner nuclear membrane (Figure 2). SUN proteins interact with multiple proteins in the nucleoskeleton, including lamins [34], which are strong candidates to retain SUN proteins at the inner nuclear membrane. An additional model postulates that the conserved SUN domain within the lumen aids in retention, presumably by forming nuclear envelope bridges [16••,23••].

Building SUN–KASH bridges 2: the interaction between SUN and KASH proteins in the perinuclear space

A direct interaction between SUN and KASH domains in the perinuclear space forms the central link of the nuclear envelope bridge [11]. Until recently, the oligomerization state of SUN proteins and the molecular interaction faces between SUN and KASH domains were not well understood [35,36]. Two new structural studies show that SUN domains assemble into clover-like trimers mediated by a triple-helix bundle of short, coiled regions at the amino end of the conserved SUN domain [16••,37].

The most significant recent contribution to the understanding of the SUN–KASH bridge came when Sosa *et al.* [16••] presented crystal structures of the interactions between human Sun2 and the KASH domains of Nesprin-1/Nesprin-2 (Figure 3). They characterized extensive interaction faces among the three SUN protomers that create three independent KASH-binding sites. The C-terminal four residues of the KASH domain are buried in a pocket within the surface of one SUN protomer, which is supported by *in vitro* studies showing that the addition of a single alanine to the end of the KASH domain disrupts binding [16••]. KASH domains then extend for 13 residues across a cleft formed by two SUN protomers and are clamped in place by a protruding β-sheet, or 'KASH-lid', from the first SUN protomer overlapping with its neighbor. Finally, the next six residues interact with the surface of the second SUN

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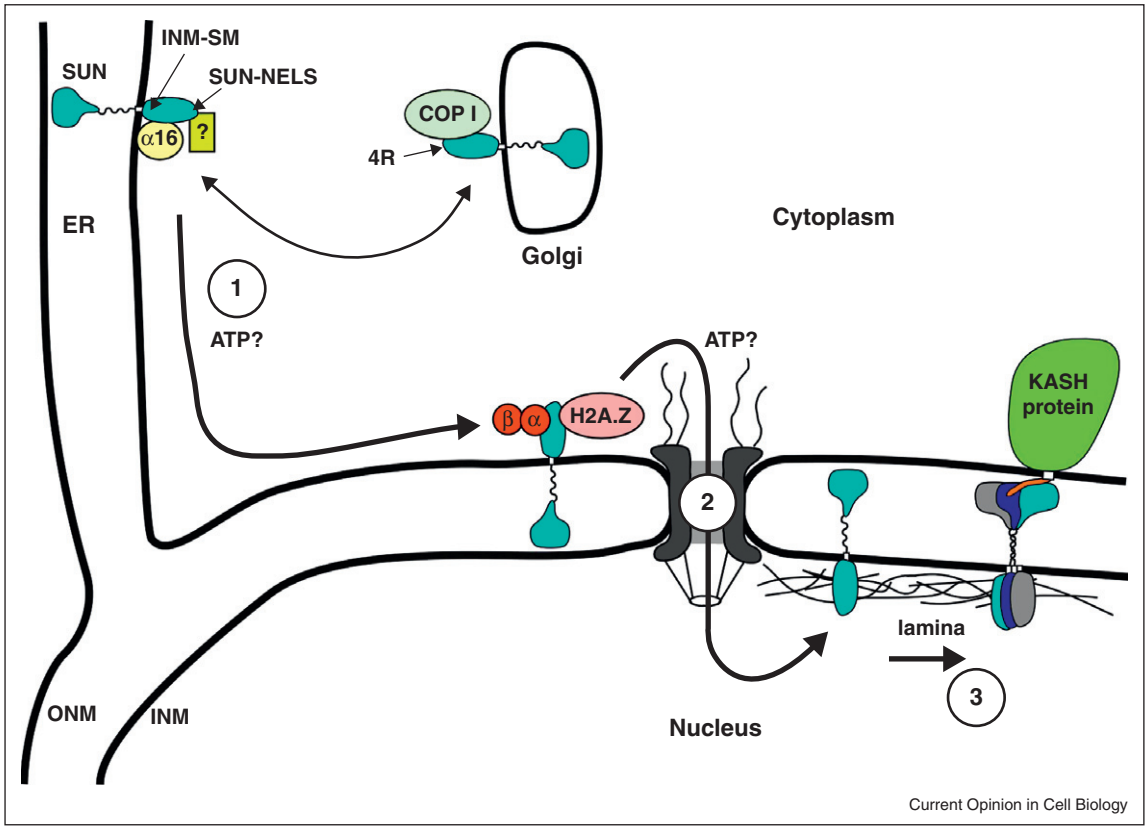
Figure 2



Three steps to targeting SUN proteins to the inner nuclear membrane (INM). First, signals including INM-SM and SUN-NELS recruit partners to move SUN proteins from the peripheral ER to the outer nuclear membrane (ONM). ATP and the Golgi retrieval signal (4R) also participate in this first step. Second, importins (red), ATP, and/or histone H2A.Z (pink) help shuttle SUN proteins across the nuclear pore. Finally, SUN proteins are retained at the INM by interacting with lamins and forming bridges with KASH proteins.

protomer. This interaction is further stabilized by the formation of an intermolecular disulfide bond between a cysteine 23 residues from the C-terminus of the KASH domain and a conserved cysteine on the surface of the SUN protein. Disulfide bond formation is dispensable for SUN–KASH binding, but is proposed to help withstand the forces transmitted across the bridge during nuclear migration or chromosome movement [16••]. The remainder of the KASH domain extends away from the SUN trimer toward the outer nuclear membrane. This high-resolution view of SUN–KASH interactions gives us the first clear picture into how they tightly interact to perform their many functions.

KASH proteins interact with microtubule motors or actin filaments to move nuclei

Once KASH proteins are recruited to the outer nuclear membrane, their cytoplasmic domains are free to mediate interactions between the nucleus and the cytoskeleton [11]. Two mechanisms for using KASH proteins to move nuclei were recently elucidated. In one mechanism, KASH proteins, including *C. elegans* UNC-83, *Drosophila* Klarsicht, and mammalian Nesprin-4 function as nuclear-specific adaptors to recruit motor proteins dynein and/or kinesin-1 to the surface of the nucleus [11,24,26••]. In these three cases, kinesin-1 provides the major forces to move nuclei along polarized microtubules. Live imaging of *C. elegans* hypodermal nuclear migrations showed that kinesin-1 moves nuclei forward, while dynein is required to roll nuclei or to move them in the reverse direction to resolve cytoplasmic roadblocks [26••]. In other systems, such as the *C. elegans* germline and early embryo, dynein is recruited to the nuclear envelope by the KASH protein ZYG-12 to position nuclei or to mediate meiotic chromosome movements and pairing [9,38]. Thus, the relative roles of the minus-end-directed microtubule-motor dynein versus the plus-end-directed motor kinesin-1 vary.

The second mechanism for moving nuclei involves KASH proteins tethering nuclei to a moving actin network. In polarizing fibroblasts, actin filaments flow away from the wound edge. The KASH proteins Nesprin-1/Nesprin-2 connect nuclei to the moving filaments [27••].

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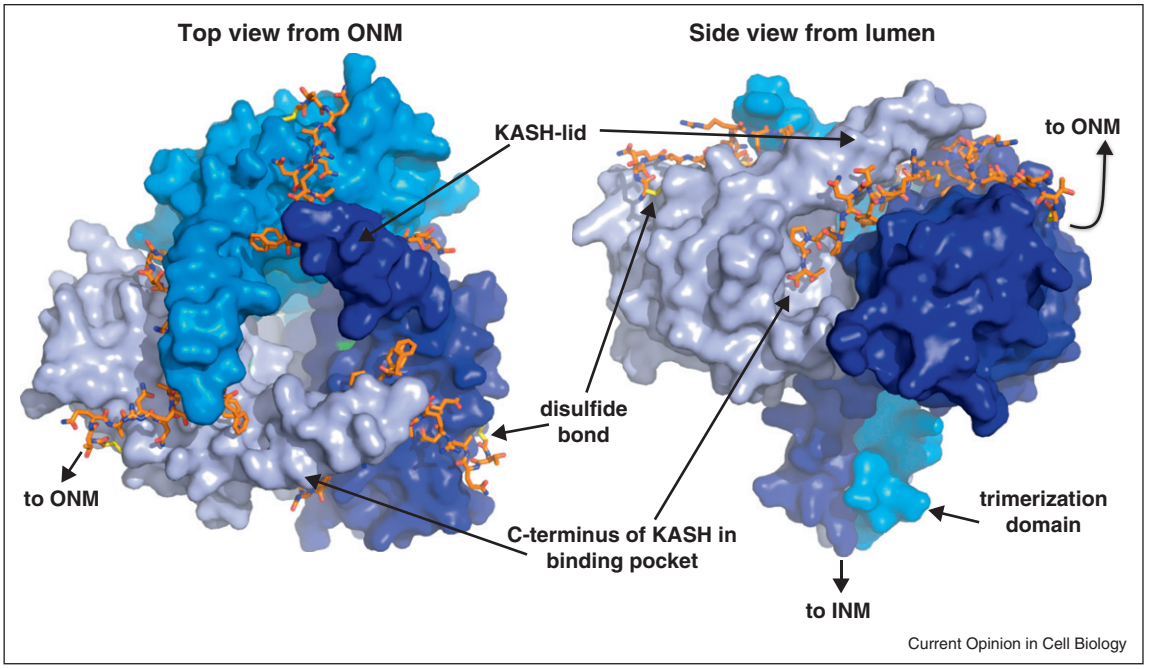
Figure 3



The crystal structure of the interaction between the SUN and KASH domains of human Sun2 and Nesprin-2. A surface representation of the three SUN protomers (shades of blue) and the backbone of the KASH peptide (orange) are shown from two angles.
Adapted, with permission, from [16].

Nesprin-1/Nesprin-2, orthologs of *C. elegans* ANC-1 and *Drosophila* MSP-300, function to tether the outer nuclear membrane to actin [11]. In addition to Nesprins, SUN proteins, the inner nuclear membrane protein Samp1, and lamin also assemble into transmembrane actin-associated nuclear (TAN) lines to complete the connection between nuclei and moving actin filaments [27••,39,40]. Together, these two examples demonstrate the variety of different mechanisms KASH proteins use to generate forces at the nuclear envelope.

The role of SUN–KASH bridges in mechanotransduction of forces across the nuclear envelope

Mechanotransduction is the translation of extracellular mechanical stimuli into chemical signals. Some mechanical stimuli are propagated through a pre-stressed cytoskeleton all the way to the nucleus [41]. SUN and KASH proteins have been hypothesized to propagate mechanical signals to the nucleus [42]. In support of this hypothesis, disruption of KASH proteins causes a loss of cellular mechanical stiffness, suggesting that nuclear envelope bridges organize the global cytoskeleton [43]. Two recent reports provide further evidence for the role of KASH proteins in mechanotransduction. First, a microneedle was used to physically pull on the cytoplasm and the displacement of the nucleus was used to approximate the strength of the mechanical coupling of the nucleus to the cytoskeleton [3•]. The disruption of SUN or KASH proteins by dominant negative constructs reduced nuclear deformation, impaired intracellular force transduction, and affected cell migration and polarization, demonstrating that SUN–KASH bridges form a connection between the cytoskeleton and nucleus that is critical for intracellular force transmission [3•]. The second report implicates the KASH protein Nesprin-3, which links intermediate filaments to the nucleus, in mechanotransduction [28•]. In the presence of siRNA against Nesprin-3, cultured endothelial cells failed to polarize or migrate upon the induction of flow [28•]. Together, these reports strongly support the hypothesis that SUN and KASH bridges function in mechanotransduction.

SUN–KASH bridges in human disease

Mutations in SUN and KASH proteins are thought to contribute to a wide variety of diseases, including cancer [11]. Here we focus on recent reports about the role of SUN proteins in laminopathies, a spectrum of diseases caused by mutations in lamins [44]. SUN and KASH proteins have long been postulated to contribute to the pathology of laminopathies [19,33••,45]. A surprising report showed that knockout of mouse Sun1 reduced the severity of phenotypes associated with mutations in lamin A in mouse models for Emery-Dreifuss Muscular Dystrophy or Hutchinson-Gilford Progeria Syndrome

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[20••]. Sun1, lamin A double mutant mice lived longer, grew larger, and had fewer defects in bone structure, muscle formation, senescence, heterochromatin marks, and the shape of nuclei than lamin A single mutant mice [20••]. Similar results were observed in cells from Progeria patients treated with siRNA against Sun1 [20••]. Thus, Sun1 enhances the defects associated with lamin A mutations in disease.

The mechanisms of how SUN proteins contribute to laminopathies are unknown, but multiple models have been proposed. Mutations in lamin A lead to less stiff nuclei [46,47], suggesting that the presence of Sun1 could lead to more pulling forces on the nuclear envelope and therefore more damage to a weakened nucleus. The other favored model is that mutations in lamins, and perhaps SUN proteins, lead to altered transcription patterns of important developmental factors [47,48]. An alternative model is that mutations in lamin A lead to overexpression of Sun1 and accumulation in the Golgi, which leads to toxicity [20••]. The newest model is that overexpression of Sun1 in lamin A mutants causes toxicity by inducing hyperactivity in the DNA damage response [5,10].

Conclusions

Great progress has been made in the past two years in understanding how the LINC complex of SUN and KASH proteins is assembled, how it functions in nuclear migration, and how it participates in mechanotransduction. It has also become clear that LINC complexes play important roles in human disease. Despite this progress, many questions remain. Many players in SUN trafficking remain to be identified, including those utilizing ATP and proteins that bind the SUN-NELS. We do not understand when or where SUN multimerization and KASH binding occurs, how complexes are rearranged during important developmental switches, or how they participate in mechanotransduction. Finally, future experiments are required to determine the relative contributions of each of the proposed models for SUN and KASH proteins in disease progression. Continued research by basic and clinical scientists should translate these findings on nuclear-cytoskeletal interactions into the treatment of human disease.

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