Bringing KASH under the SUN: the many faces of nucleo-cytoskeletal connections

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The nucleus is the most prominent cellular organelle, and its sharp boundaries suggest the compartmentalization of the nucleoplasm from the cytoplasm. However, the recent identification of evolutionarily conserved linkers of the nucleoskeleton to the cytoskeleton (LINC) complexes, a family of macromolecular assemblies that span the double membrane of the nuclear envelope, reveals tight physical connections between the two compartments. Here, we review the structure and evolutionary conservation of SUN and KASH domain–containing proteins, whose interaction within the perinuclear space forms the "nuts and bolts" of LINC complexes. Moreover, we discuss the function of these complexes in nuclear, centrosomal, and chromosome dynamics, and their connection to human disease.

Nucleus and chromosome movement are essential macroscopic manifestations of complex molecular events involving anchors, motors, and the cytoskeleton. In this review, we will describe how Sad1/UNC-84 (SUN) and Klarsicht/ANC-1/Syne-1 homology (KASH) domain–containing protein families confer a range of previously unsuspected functional versatilities to the nuclear envelope (NE) in order to display such prowess. We will also discuss the current evidence for the involvement of these proteins in human pathologies.

Setting the stage: the NE

The NE is composed of two lipid bilayers, the inner and the outer nuclear membrane (INM and ONM, respectively), which are connected at nuclear pores, thus delineating the perinuclear space (Fig. 1). The ONM is an extension of the rough ER, and the INM adheres to the nuclear lamina, a meshwork of type-V intermediate filaments composed of A- and B-type lamins

(Stuurman et al., 1998; Hutchison, 2002). In contrast to other intermediate filaments, all lamins harbor a nuclear localization signal, and B-type lamins retain a farnesyl group through which they associate with the INM. Although A-type lamins are developmentally regulated, B-type lamins are essential for cell viability (Lenz-Böhme et al., 1997; Sullivan et al., 1999; Liu et al., 2000; Vergnes et al., 2004). Although the higher order of lamin assembly has not been established in mammalian cells, the supramolecular organization of the 10-nm B-type lamin filament has been determined in *Caenorhabditis elegans* (Ben-Harush et al., 2009). Overall, the nuclear lamina appears to form a compressed network that functions as a "molecular shock absorber" (Dahl et al., 2004; Panorchan et al., 2004).

The nuclear lamina fulfills many diverse regulatory functions (Gruenbaum et al., 2000). Accordingly, A-type lamins bind to a myriad of architectural, chromatin, gene-regulatory, and signaling proteins (Moir and Spann, 2001; Zastrow et al., 2004). The nuclear lamina interacts directly with the nucleoplasmic domains of single and multitransmembrane INM proteins (Burke and Stewart, 2002) such as the lamin B receptor (Worman et al., 1988), lamin-associated peptides 1 and 2 (Foisner and Gerace, 1993), emerin (Bione et al., 1994), and Man1 (Lin et al., 2000). Hence, these proteins display decreased lateral diffusion across the INM and a characteristic nuclear rim-like pattern in immunofluorescence microscopy (Soullam and Worman, 1995; Ellenberg and Lippincott-Schwartz, 1999; Holmer and Worman, 2001; Lusk et al., 2007).

Proteomic analyses of the NE (Schirmer et al., 2003) suggest the existence of no less than 60 novel putative INM proteins, which indicates that our picture of the NE is still incomplete. The up-regulation of some of these proteins during cellular differentiation (Chen et al., 2006) stresses the need to fully characterize their structure and function to obtain a more integrated view of the NE.

### The rise of the SUN domain: identification and evolutionary conservation

Studies of mutant *C. elegans* embryos with defects in nuclear migration and anchorage led to the identification of UNC-84, a transmembrane protein of the NE (Fig. 2 A; Malone et al., 1999).

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Figure 1. Topology and functions of LINC complexes. In the perinuclear space, the evolutionarily conserved interaction between SUN (orange oval) and KASH (green) domain–containing proteins physically connects the nuclear lamina to essential cytoskeletal elements such as the actin and microtubule networks. These connections enable nuclear migration or anchorage at specific locations within cells and syncytia. SUN–KASH interactions also play essential roles in chromosome dynamics and tethering at the NE.
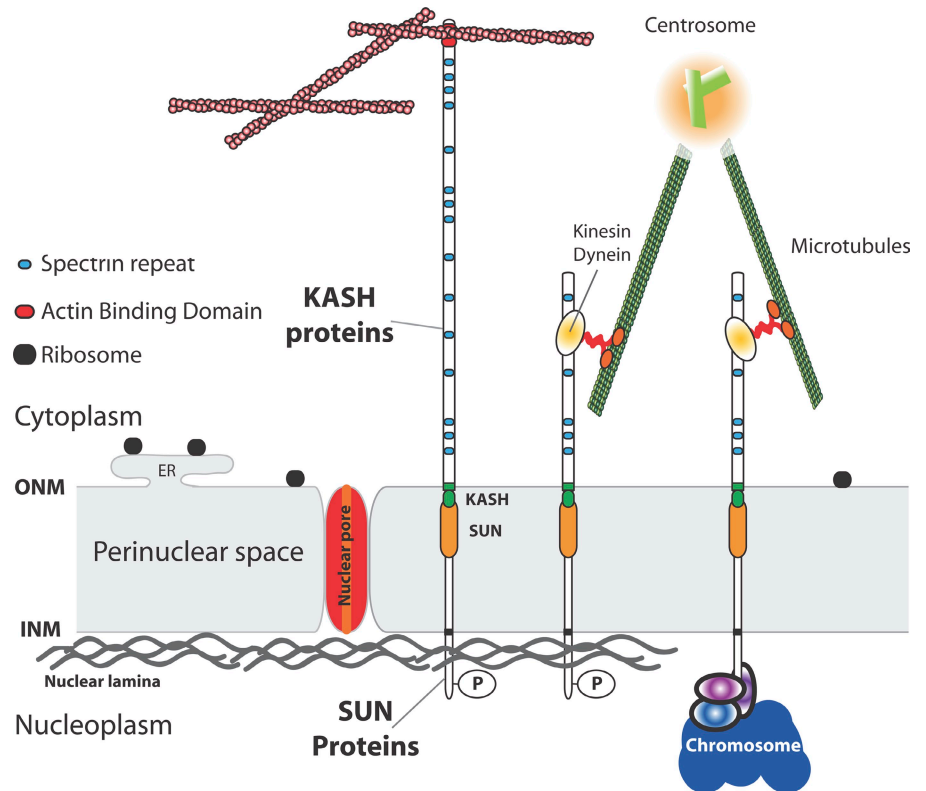
UNC-84 harbors the so-called SUN domain that consists of a stretch of ∼150 C-terminal amino acids. The SUN domain was also detected in the *Schizosaccharomyces pombe* Sad1 protein that was originally identified as a spindle pole body (SPB) component (Hagan and Yanagida, 1995) as well as in two predicted mammalian transmembrane proteins called Sun1 and Sun2. Sun1 and Sun2 were further characterized as ubiquitously expressed integral type II transmembrane proteins of the NE with a nucleoplasmic N-terminal region and a C-terminal region protruding into the perinuclear space (Hodzic et al., 2004; Crisp et al., 2006; Haque et al., 2006; Wang et al., 2006). This topology therefore positioned the SUN domain within the perinuclear space (Fig. 1). The SUN domain is also found in three other transmembrane mammalian proteins: Sun3, SPAG4, and SPAG4L (Fig. 2 B). However, their expression pattern is more restricted than Sun1 and Sun2. Sun3 is predominantly detected in testes and mostly localizes in the ER (Crisp et al., 2006). SPAG4 is expressed in spermatids, where it localizes to the manchette and axoneme (Shao et al., 1999), in pancreas and in testes. Its expression is also switched on and up-regulated in neoplastic tissues (Kennedy et al., 2004). SPAG4L mRNA (also called TSARG4) has been reported in a wide range of adult mouse tissues (Xing et al., 2003), but its localization remains unknown.

SUN domains display remarkable evolutionary conservation. They are found in *D. melanogaster* Klaroid and Giacomo (Kracklauer et al., 2007), in *Saccharomyces cerevisiae* Mps3 (Jaspersen et al., 2006), and in plants (Fig. 2 B and Table I) such as in the rice protein OzSAD1 (Moriguchi et al., 2005). The broad evolutionary conservation of SUN domains suggests that they participate in essential biological functions.

Interaction of Sun proteins with the nuclear lamina

The C-terminal SUN domain of both Sun1 and Sun2 protrude into the perinuclear space, whereas their N-terminal region is nucleoplasmic and interacts directly with A- and B-type lamins (Fig. 1; Hodzic et al., 2004; Crisp et al., 2006; Haque et al., 2006; Wang et al., 2006). The NE retention of Sun1 does not require A- or B-type lamins, whereas a significant proportion of Sun2 mislocalizes from the NE to the ER in fibroblasts lacking A-type lamins (Crisp et al., 2006; Haque et al., 2006; Hasan et al., 2006). The existence of differential retention mechanisms in mammalian cells is further supported by the colocalization of Sun1, but not of Sun2, with nuclear pore components (Liu et al., 2007). In *C. elegans* embryos lacking Ce-lamin, UNC-84 completely "drifts" from the NE to the ER (Lee et al., 2002), whereas SUN-1/MTF-1, the other *C. elegans* Sun protein (Fig. 2 B), remains at the NE (Fridkin et al., 2004), which further supports differential NE retention mechanisms of SUN domain–containing proteins. Little is known about the regulation of the interaction between Sun proteins and the nuclear lamina. Interestingly, Sun2 is heavily phosphorylated on three serine residues (Ser-12, Ser-54, and Ser 116) upon treatment of HeLa cells with phosphatase inhibitors (Grønborg et al., 2002). Analysis of the regulation of phosphorylation and O-glycosylation of Sun proteins may provide key information regarding their nucleoplasmic interaction networks and localization mechanisms at the NE.

Bringing some KASH under the SUN: assembly of LINC complexes

Several ONM proteins that interact with SUN domains were identified in multiple organisms (Fig. 3 A and Table I). These

A

Hyp7 cell

		Migration	Anchorage
Wild-type		DM	
unc-84			
unc-83			
anc-1			

UNC-84::GFP

B

```
                QARAIVN--SALKLYSQD---KTGMVDFALESGGGSILSTRCSETYETKT-----ALMSLFGIPLWYFS-QSPRVVIQPDIY---PGNCWAFK-GSQ
Hs Sun1
Hs Sun2         QVHHIVK--QALQRYSED---RTGLADYALESGGASVISTRCSETYETKT-----ALLSLFGIPLWYHS-QSPRVILQPDVH---PGNCWAFQ-GPQ
Hs Sun3         EVSNLVN--YVLKKLRED---QVEMADYALKSAGASIIEAGTSESYKNNK-----AKLYWHGIGFLNHE-MPPDIILQPDVY---PGKCWAFP-GSQ
Hs Spag4             VAK--LVFQRLNED---FVRKPDYALSSVGASIDLQKTSHDYADRN-----TAYFWNRFSFWNYA-RPPTVILEPHVF---PGNCWAFE-GDQ
Hs Spag4L            AQ--KIMKMIHGD---YIIEKPDFALKSIGASIDFEHTSVTYNHEK-----AHSYWNWIQLWNYA-QPPDVILEPNVT---PGNCWAFE-GDR
Ce UNC-84       HLEAIIR--QMIYEYDTD---KTGKVDYALESSGGAVVSTRCSETYKSYT-----RLEKFWDIPIYYFH-YSPRVVIQRNSKSLFPGECWCFK-ESR
Ce Sun-1/MTF-1  PTASLPPSSQ-LQPMHITRR---ALLGVNVANSLIGASIDHSCSSRPVSAKD------GFFYDFMSYFGTF-QEGYALLDRDVLS--PGEAWCTY-DKR
Dm Klaroid      EVRQIVK--TVLAIYDAD---KTGLVDFALESAGGQILSTRCIESYQTKS-----AQISVFGIPLWYPT-NTPRVAISPNVQ---PGECWAFQ-GFP
Dm Giacomo            VA--LAKPRIN---------YASEELGARIINVKAHSIDGTNI--------IRSLLGLDFST-NPPVNMIRTGLS---PGSCFGFN-GSR
Sp Sad1         DWKFFIE--STVRKYLTD---PVSMPNFALLSTGAEVLPALTSKRYVRRPSAFIPRFTSYFFDSLVVRG-HEPSIALTPNNA---VAMCWSFQ-GSE
Sc Mps3         QYSSILMKRLIHQIYNSNQHQWEDDLDFATYVQGTKLLNHLTSPIWRQGS-----GVQPIELLTDSKQSSSTYWQCENE---PGCSWAIRFKTP
Os Sad1         FAKEIVE--METIERHAAD---GLGMVDYALASGGG--KVVKHSEAFRKAK-----SFMPSRNSLL-EQAKKMLEPSFGQ--PGECFALQ-GSS

Hs Sun1         GYL-VVRLSMMIHPAAFTLEHIPKT-----LSPTGNISSAPKDFAVYGLENEYQEEG-------QLLGQFTYDQDG----ESLQMFQALK--RPDDTA
Hs Sun2         GFA-VVRLSARIRPTAVTLEHVPKA-----LSPNSTISSAPKDFAIFGFDEDLQQEG-------TLLGKFTYDQDG----EPIQTFHFQ---APTMAT
Hs Sun3         GHT-LIKLATKIIPTAVTMEHISEK-----VSPSGNISSAPKFVYKHCCEGEE-------IFLGQFIYNKTG----TTVQTFELQ--HAVSEY
Hs Spag4        GQV-VIQLPGRVQLSDITLQHPPPS-----VEHTGGANSAPRDFAVFGLQVYDETE-------VSLGKFTFDVEK----SEIQTFHLQ---NDPPAA
Hs Spag4L       GQV-TIQLAQKVYLSNLTLQHIPKT-----ISLSGSLDTAPKDFHIYGMEGSPKEE-------VFLGAFQFQPF----NIIQMFPLQ---NQPARA
Ce UNC-84       GYI-AVELSHFIDVSSISYEHIGSE-----VAPEGNRSSAPKGVLVWAYKQIDDLNSR------VLIGDYTYDLDG----PPLQFFELAK--HKPDFP
Ce Sun-1/MTF-1  ATL-TVKLARFVIPKSVSYQHVRWSG-----IVPN----HAPKLYDVVACTDSCCTKWQ-----PLVANCEYKERDGSYDEQEQFCSVPT--IQNHSP
Dm Klaroid      GFLGKSRLNSLVVYVTGFTLEHIPKS-----LSPTGNISSAPRNFTVWGLQEQKDQEP------VLFGDYQFEDNG----ASLQYFAVQN--LDIKRP
Dm Giacomo      ATV-TLHLARTIIVEAITLTHVARE-----MTPDLCVKSAPKNFDGLRSENS-KRE--------LLGQWSYDNAAN--KRTQSYSVR------SDTF
Sp Sad1         GQL-GISLSRPVYVTNVTIEHVQHK------IAHD--LSSAPKDFELWVQGMSSKMF-------VLLGKARYSLTE---DSIQTFSFESSNYIVAEP
Sc Mps3         LYLTKISYMHGRFTNNLHIMNSAPRLISLYVKLSQTKEIKALQTLANQYGFGQHHKRDRN-----YIKIAKFEYRLTDS--RIRQQMYLPPWFIQLKPL
Os Sad1         GYV-EIKLRTGTIIPEAVSLEHVDKS-------VAYD--RSSAPKDFQVSGWYEGPEDDSDKESRVVTNLGEFSYDLEK----NNAQTFQLER--TADSRV

Hs Sun1         FQIVELRIFSNWGHPEYTCLYRFRVHGEPVK
Hs Sun2         YQVVELRILTNWGHPEYTCIYRFRVHGEPAH
Hs Sun3         LLCVKLNIFSNWGHPKYTCLYRFRVHGTPGKHI
Hs Spag4        FPKVKIQILSNWGHPRFTCLYRVRAHGVRTSEGAEGSA-QGPH
Hs Spag4L       FSAVKVKISSNWGNPGFTCLYRVRVHGSVAPPREQ------PHQN
Ce UNC-84       VKFVELEVTSNYGAPI-FTCLYRLRVHGKVVQVCE
Ce Sun-1/MTF-1  INHVQFRFRENHGDMPKTCAYLIRVYYGEPVDPPKE----TQPMTD
Dm Klaroid      YEIVELRIIETNHGHPTYTCLYRFRVHGKPPAT
Dm Giacomo      FRNLDFSFNSNHGAN-STCIYRVEVYGRL
Sp Sad1         IQNVILKTKSNWGNPNYTCLYRFRVHGTVPNADEQ----PIPSLG
Sc Mps3         VRSIVFQVDENYGNKKFISLRKFIINGVTPQDLQIIENNEFPVLL
Os Sad1         INMVRLDFCSNHGNSELTCIYRFRVHGREPGSPS
                     *  *                    *
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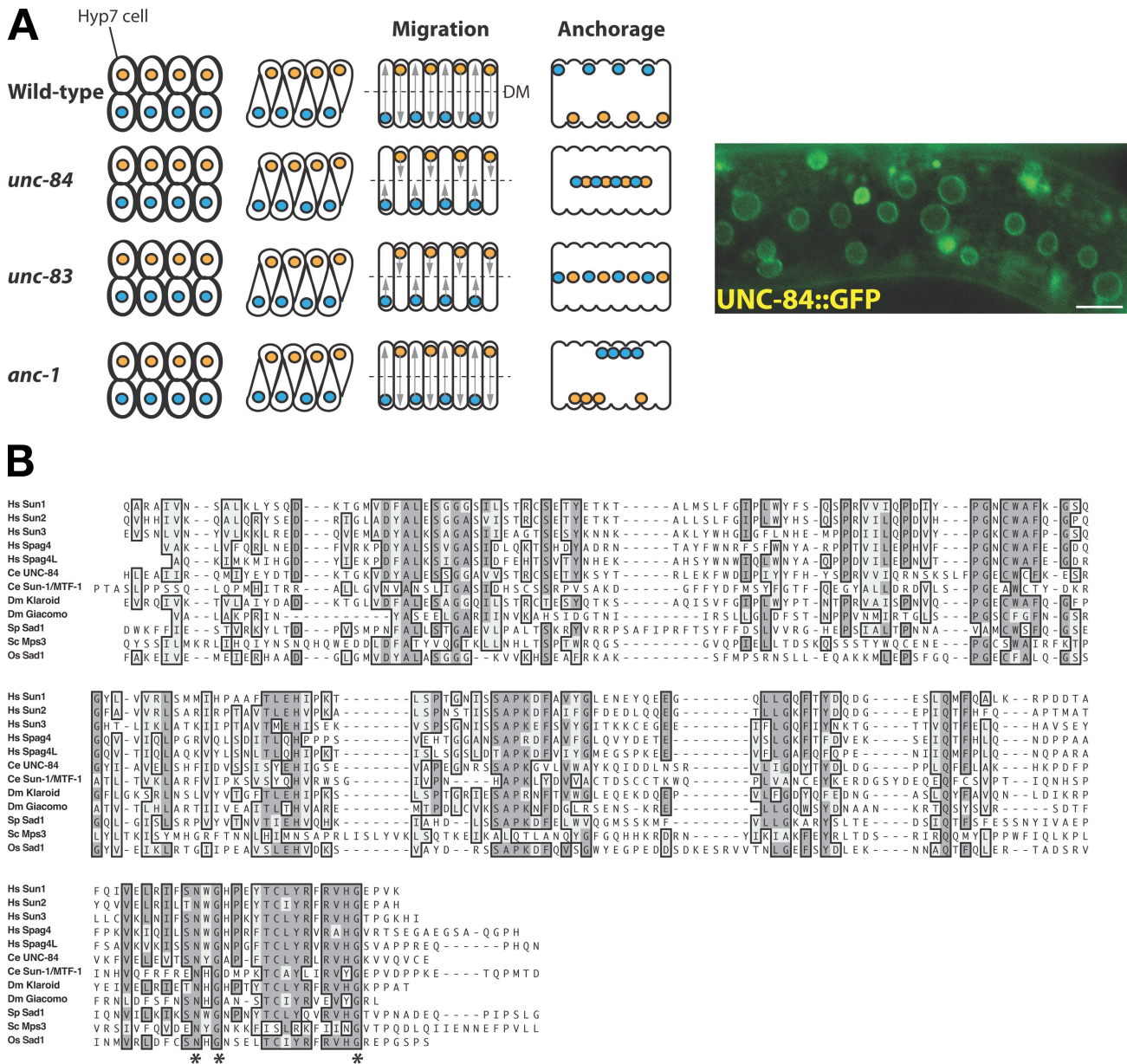
Figure 2. **Identification of Sun proteins.** (A) SUN and KASH proteins are required for nuclear dynamics in hypodermal syncytium of *C. elegans* embryos. In wild-type animals, syncytium formation is preceded by the contralateral migration of Hyp7 nuclei (arrows) across embryos dorsal median (DM). Nuclei are then anchored in the newly formed syncytium. *Unc-84* mutants fail in both nuclear migration and anchorage, whereas *unc-83* and *anc-1* mutants display nuclear migration and nuclear anchorage defects, respectively. Dorsal cord location of failing migratory nuclei is caused by passive displacement of wall muscles squeezing the hypodermis. (right) Localization of EGFP::UNC-84 to the NE in *C. elegans* embryos. The image is reproduced with permission from *Development* (Malone et al., 1999). Bar, 10 µm. (B) Alignment of evolutionary-conserved SUN domains. Dark gray– and light gray–shaded residues correspond to the conservation of identical or similar residues, respectively. Asterisks indicate strictly conserved amino acids.

are *D. melanogaster* Klarsicht and Msp-300 (Fischer-Vize and Mosley, 1994; Rosenberg-Hasson et al., 1996; Welte et al., 1998); *C. elegans* ZYG-12 (Malone et al., 2003), UNC-83 (Starr et al., 2001), and ANC-1 (Starr and Han, 2002); and mammalian Syne-1 and -2, also called Nesprin-1 and -2 (both terms will be used in this review; Apel et al., 2000). These are all integral type II transmembrane proteins that localize at the ONM and share an evolutionarily conserved C-terminal region: the KASH domain (Starr and Han, 2002). This domain consists of a transmembrane region followed by an evolutionary-conserved stretch of ~35 amino acids protruding into the perinuclear space

(Fig. 3, A and B). KASH domains have been identified in many organisms, from yeasts to mammals (Table I).

Linkers of the nucleoskeleton to the cytoskeleton (LINC) complexes designate the macromolecular assemblies that form through SUN–KASH interactions (Crisp et al., 2006) and span both the INM and ONM, thereby establishing physical connections between the nucleoplasm and the cytoplasm (Figs. 1 and 3 A). SUN domain–containing proteins are essential to recruit KASH domain proteins at the ONM. Indeed, ANC-1 and UNC-83 fail to localize at the ONM in UNC-84 mutants (Starr et al., 2001; Starr and Han, 2002; McGee et al., 2006), and ZYG-12 requires SUN-1/MTF-1

Table I. **Functional diversity of SUN and KASH domain proteins**

| Organism | Nucleoplasm | Perinuclear space | | Cytoplasm | | Function | References |
		SUN	KASH	Motor	Cytoskeleton		
C. elegans	Ce-lamin	UNC-84	UNC-83	Kinesin1	MT	Nuclear migration	Starr et al., 2001; Meyerzon et al., 2009
C. elegans	Ce-lamin	UNC-84	ANC-1	NA	Actin	Nuclear anchorage	Malone et al., 1999; Starr and Han, 2002
C. elegans	Ce-lamin	SUN-1/MTF-1	ZYG-12	Dynein	Centrosome	Centrosome tethering at NE	Malone et al., 2003
C. elegans	Ce-lamin	SUN-1/MTF-1	ZYG-12	Unknown	Unknown	Meiotic chromosome dynamics	Penkner et al., 2007
D. melanogaster	LamDm0	Klaroid	Klarsicht	Dynein	MT	Nuclear migration	Mosley-Bishop et al., 1999; Kracklauer et al., 2007
H. sapiens	Lamin A/C-B1	Sun1/2	Syne-1/2	NA	Actin	Nuclear anchorage	Grady et al., 2005; Zhang et al., 2007b; Méjat et al., 2009; Lei et al., 2009
H. sapiens	Lamin A/C-B1	Sun1/2	Nesprin-3	NA	Plectin	Nuclear coupling to IF	Wilhelmsen et al., 2005
H. sapiens	Lamin A/C-B1	Sun1/2	Nesprin-4	Kinesin1	MT	Nuclear migration	Roux et al., 2009
S. pombe	Bqt1/2	Sad1	Kms1/2	Dynein	MT	Meiotic chromosome dynamics	Chikashige et al., 2006; Miki et al., 2004
S. pombe	Ima1, Ndc80	Sad1	Kms2	Unknown	MT	Centromere-SPB coupling	King et al., 2008
S. cerevisiae	Ndj1	Mps3	Unknown	Unknown	Unknown	Meiotic chromosome dynamics	Conrad et al., 2008
S. cerevisiae	Sir4	Mps3	Unknown	Unknown	Unknown	Mitotic telomere tethering at NE	Bupp et al., 2007
S. cerevisiae	Unknown	Mps3	(Mps2)	Unknown	SPB	SPB tethering at NE	Jaspersen et al., 2006

The various physiological functions of protein networks based on SUN/KASH interactions across the NE are listed horizontally. The localization (nucleoplasm, perinuclear space, or cytoplasm) of each network components as well as the nomenclature of SUN and KASH proteins among different species are indicated. Mps2 is in parentheses because it does not contain any detectable KASH domain even though it is involved with Mps3 in SPB tethering at the NE in *S. cerevisiae*. MT, microtubule; NA, not applicable.

for its NE localization (Malone et al., 2003). In *D. melanogaster*, Klaroid is strictly required for the ONM localization of Klarsicht and Msp-300 (Kracklauer et al., 2007; Technau and Roth, 2008). Similarly, the simultaneous siRNA-mediated down-regulation of both mammalian Sun1 and Sun2 prevents the localization of Nesprin-2–giant at the NE (Padmakumar et al., 2005; Crisp et al., 2006). The expression of either the recombinant SUN domain of Sun1 and Sun2 within the ER lumen or the KASH domain of Nesprin-1, -2, and -3 invariably results in the displacement of all endogenous NE spectrins (Nesprins) from the NE to the ER (Padmakumar et al., 2005; Crisp et al., 2006; Stewart-Hutchinson et al., 2008). Coupled with the observation that the KASH domain of Nesprin-1, -2, and -3 is equally able to interact with both Sun1 and Sun2, SUN–KASH interactions seem promiscuous (Stewart-Hutchinson et al., 2008). In mammalian cells, SUN–KASH interactions strictly require the C-terminal polyproline motif of KASH domains (Fig. 3 B; Padmakumar et al., 2005; Ketema et al., 2007) as well as the last 20 C-terminal amino acids of the SUN domain, which contains three strictly conserved amino acid residues (Fig. 2 B; Stewart-Hutchinson et al., 2008). Consistent with the proposed interaction between Sun proteins and Nesprins across the NE, disruption of LINC complexes provokes a significant enlargement of the perinuclear space between the ONM and the INM (Crisp et al., 2006). As we will see, in addition to widening the landscape of known NE proteins, the discovery of LINC complexes has radically redefined our view of NE function (Stewart et al., 2007).

Providing functional diversity to the NE: the many faces of KASH proteins

In the following paragraphs, we describe the functional aspects of various KASH domain-containing proteins in different organisms. KASH domains provide a generic NE tethering device for functionally distinct proteins whose cytoplasmic domains mediate nuclear positioning, maintain physical connections with other cellular organelles, and even influence chromosome dynamics (Fig. 1 and Table I).

Nuclear anchorage to the cytoskeleton. The direct "harpooning" of the cytoskeleton with a micropipette tip results in a direct and immediate force transfer to the nucleus, whose NE locally extends and moves in the direction of the pull (Fig. 4 A). This effect is microtubule independent and suggests that the nucleus is "hard-wired" to the cytoskeleton (Maniotis et al., 1997; Wang et al., 2009). As shown in Fig. 4 B, *C. elegans* ANC-1, *D. melanogaster* Msp-300, and the giant isoforms of mammalian Nesprin-1 (also called Syne-1 [Apel et al., 2000], Myne1 [Mislow et al., 2002], and Enaptin [Padmakumar et al., 2004]) and Nesprin-2 (also called Syne-2 [Apel et al., 2000] and NUANCE [Zhen et al., 2002]) are gigantic proteins localizing to the ONM, and they are predicted to extend as a rod-like structure of up to 300–400 nm into the cytoplasm (Zhang et al., 2002). They all share a common architecture: an N-terminal actin-binding domain and interspersed spectrin repeats. The latter are triple-helical coiled-coil domains with elastic properties that might be important in terms of deformability (Lenne et al., 2000).
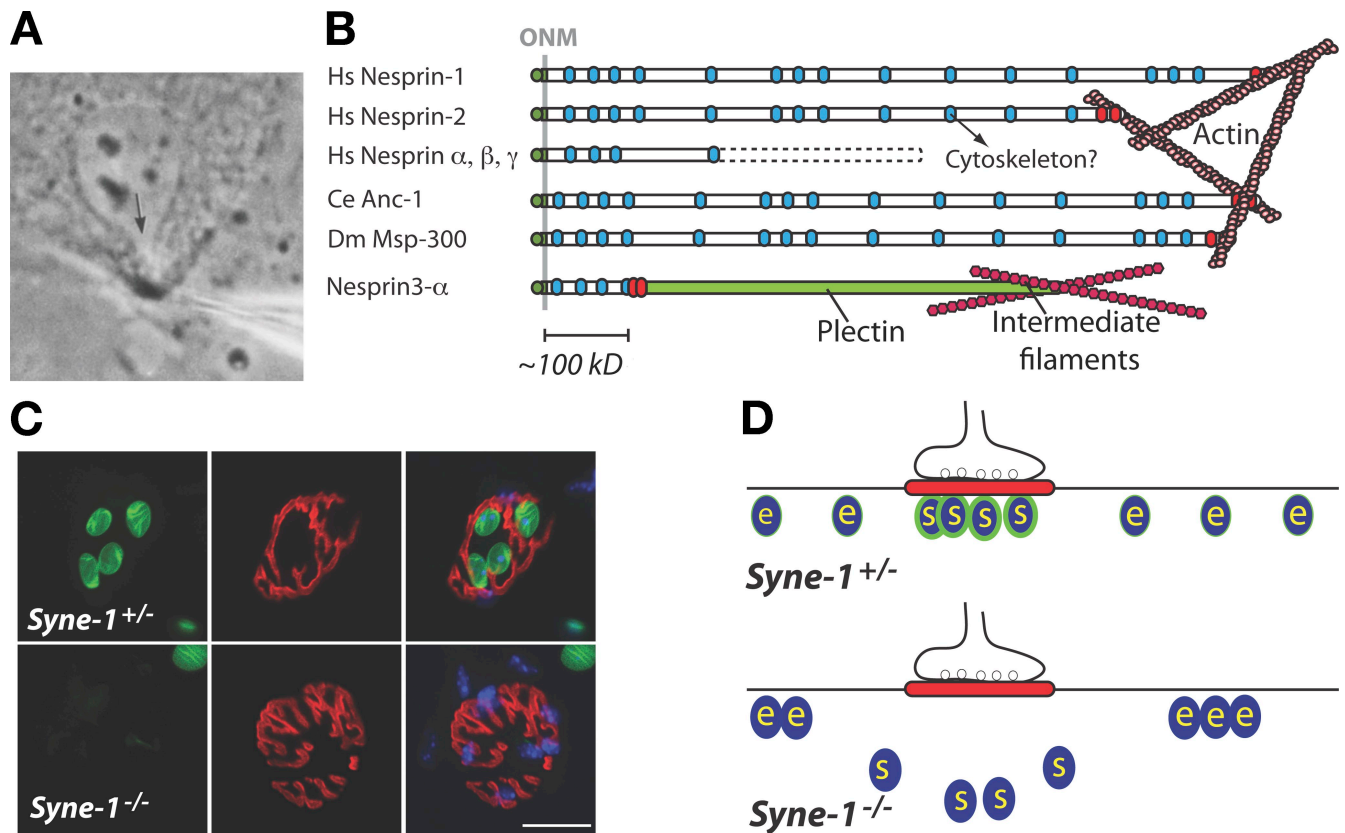
Figure 3. Identification of KASH proteins. (A) Topological depiction of INM SUN and ONM KASH proteins in various organisms. Alternative names of a unique protein are separated by slashes. (B) Alignment of evolutionarily conserved KASH domains that consist of a transmembrane domain and an ~30–amino acid luminal domain. Dark gray– and light gray–shaded residues correspond to the conservation of identical or similar residues, respectively.

The actin-binding domain of Nesprin-2 is essential for the NE morphology of primary dermal fibroblasts and keratinocytes (Lüke et al., 2008). In Cos7 cells, depolymerization of the actin network rapidly induces an irregular nuclear shape and partial colocalization of Nesprin-2 with disassembled actin-rich foci (Zhen et al., 2002).

In *C. elegans*, mutation of ANC-1 or the overexpression of its actin-binding domain specifically affect nuclear anchorage within hypodermal syncytia (Fig. 2 A; Starr and Han, 2002). A missense mutation of the giant *D. melanogaster* Msp-300 protein was initially found to prevent the anchorage of nurse cell nuclei during cytoplasm dumping in *Drosophila* oocytes (Yu et al., 2006), but recent studies have questioned the involvement of Msp-300 in that phenotype (Technau and Roth, 2008; Xie and Fischer, 2008). Nevertheless, different mouse models now clearly support the role of Nesprins in anchorage of mammalian nuclei in vivo. Skeletal muscle provides an ideal readout for nuclear anchorage; an average of four so-called synaptic nuclei are tightly anchored beneath arrays of acetylcholine receptors (AchRs) at the postsynaptic apparatus (Fig. 4 C, top). Extrasynaptic nuclei, however, are interspersed along the muscle fiber (Fig. 4 D, top; Bruusgaard et al., 2003). Transgenic dominant-negative synaptic NE (Syne) mice, which express a Syne-1 KASH domain under the control a muscle-specific promoter, display a loss of synaptic nuclear anchorage beneath the AchR array and partial mislocalization of endogenous Syne-1 from the NE (Grady et al., 2005). The homozygous deletion of the KASH domain of Syne-1 led to a more severe synaptic nuclei displacement in addition to the aggregation of extrasynaptic nuclei (Fig. 4, C and D, bottom). An accompanying phenotype consists of the extensive branching of phrenic nerves, which indicates that synaptic nuclear anchorage may be essential to maintenance of innervation sites. The homozygous deletion of the KASH domain of Syne-2, however, does not affect nuclear anchorage, which indicates that Syne-1 specifically undertakes that function. Mice carrying homozygous deletions of both Syne-1 and Syne-2 die at birth due to respiratory failure (Zhang et al., 2007b).

The effect of homozygous deletions of Sun proteins on nuclear anchorage was also examined. In *Sun1*$^{-/-}$ mice, there is a modest but significant decrease of synaptic nuclei anchorage, whereas the homozygous deletion of the SUN domain of Sun2 has no effect. *Sun1; Sun2* double knockout mice die soon after birth, but this perinatal lethality phenotype can be rescued by the neuron-specific expression of Sun1 in these mice. In the latter mouse model, adult mice display a drastic loss of synaptic nuclei anchorage. This effect is also observed in embryonic day 18.5 *Sun1; Sun2* double knockout embryos. These results indicate a partially redundant role for Sun1 and Sun2 in synaptic nuclear anchorage (Lei et al., 2009). In agreement with this idea, Syne-1 localization at the NE of myonuclei was completely lost only in mice lacking both Sun1 and Sun2 (Lei et al., 2009). Together, these results indicate that, in vivo, SUN–KASH interactions are essential to connect the nuclear lamina to the perinuclear cytoskeleton and play an essential role in nuclear anchorage of mammalian synaptic and extrasynaptic nuclei. It is noteworthy that even though synaptic nuclei are transcriptionally specialized for postsynaptic components, the localization and organization of pre- and postsynaptic components appears normal in both *Syne-1; Syne-2* (Zhang et al., 2007b) and *Sun1; Sun2* double knockout mice (Lei et al., 2009).

Because spectrin repeats provide interacting interfaces with the cytoskeletal network (Djinovic-Carugo et al., 2002), other KASH domain–containing proteins that do not contain any actin-binding domains could still be significantly involved in nuclear positioning. This is illustrated by mammalian Nesprin-3. The *Nesprin-3* gene encodes two isoforms of a smaller ~100-kD protein: Nesprin-3α and β. The N-terminal spectrin repeat of Nesprin-3α interacts with the actin-binding domain of plectin (Wilhelmsen et al., 2005; Ketema et al., 2007), a cytoskeletal adaptor protein belonging to the plakin family (Fig. 4 B; Jefferson et al., 2004). Because of the alternative splicing of the interacting spectrin repeat, Nesprin-3β does not interact with plectin. The discovery of Nesprin-3 and the plectin binding specificity of the α isoform indicate that: (1) smaller Nesprins can "team up" with large cytoskeletal adaptors to connect the NE to the cytoskeleton and (2) the alternative splicing of a single spectrin repeat motif can drastically affect the biochemical properties of Nesprins. Hence, N-terminally truncated α, β, and γ isoforms of Nesprin-1 and -2 (for review see Warren et al., 2005), which

Figure 4. **KASH domain–containing proteins anchor the nucleus to the cytoskeleton.** (A) "Harpooning" of the cytoplasm induces indentations of the nucleus (arrow) in the direction of the pull, illustrating the wiring of the nucleus to the cytoskeleton. Image reproduced from Maniotis et al. (1997), copyright (1997) the National Academy of Sciences, USA. (B) Schematic depiction of KASH domain–containing proteins involved in nuclear anchorage to the cytoskeleton. Actin-binding domains (red ovals) of giant KASH proteins interact with the actin network. Blue ovals, spectrin repeats that potentially bind and organize the cytoskeleton. (C) Syne-1 mediates the anchorage of synaptic nuclei in mouse skeletal muscle. Synaptic nuclei (stained with Sun2, green) are anchored just beneath the AchR array (stained with bungarotoxin, red) in Syne-1$^{-/+}$ skeletal muscle (top). In Syne-1$^{-/-}$ skeletal muscle (bottom), anchorage of these nuclei under AchR arrays is lost. The image is reproduced with permission from *Development* (Zhang et al., 2007b). Bar, 25 µm. (D) Rendering of nuclear positioning defects observed in Syne-1$^{-/-}$ mouse skeletal muscle. (D, top) synaptic (s) nuclei, intimately associated with AchR arrays (red), abundantly express Syne-1 (green). Extrasynaptic (e) nuclei are regularly interspersed along the muscle fiber and express Syne-1 to a lower extent. (D, bottom) In the absence of Syne-1 expression, synaptic nuclei are no longer associated with the AchR array while extrasynaptic nuclei coalesce.

are generated through the combination of alternative splicing and/or promoter usage, lack an actin-binding domain but might still provide significant nuclear anchoring functionalities to the cytoskeleton (Fig. 4 B). Together, these observations indicate that LINC complexes are essential NE scaffolding, whose "inner core," the SUN–KASH interaction, "zips" the nuclear lamina to the perinuclear cytoskeleton (Starr and Fischer, 2005; Tzur et al., 2006b; Wilhelmsen et al., 2006).

Nuclear migration. Mutation of the KASH protein UNC-83 specifically prevents the migration step of hyp7 nuclei during the formation of the hypodermal syncytium (Fig. 2 A; Starr et al., 2001). Similarly, mutation of Klarsicht prevents nuclear apical migration of photoreceptor precursors in the developing eye disc of *D. melanogaster* (Fig. 5 A). This phenotype results from the uncoupling between the centrosome and the NE (Fischer-Vize and Mosley, 1994; Mosley-Bishop et al., 1999; Fischer et al., 2004). Remarkably, and in agreement with the requirement of Klaroid for the NE recruitment of Klarsicht, Klaroid mutants (*koi*) display a similar phenotype (Kracklauer et al., 2007). By the same token, nonsense or frameshift mutations of *D. melanogaster* B-type lamin encoded by *LamDm₀*

also display nuclear migration defects (Patterson et al., 2004). These results clearly indicate the requirement of the SUN–KASH interaction in nuclear migration. *Klar* also encodes a KASH-less spliced variant termed Klarsicht-LD. This protein associates with and mediates the microtubule-dependent bidirectional movement of lipid droplets in early embryos (Guo et al., 2005), illustrating the remarkable NE specification provided by KASH domains.

Nuclear migration defects were first identified in filamentous fungi nearly 35 yr ago (Morris, 2000). The *Nud* (nuclear distribution genes in *Aspergillus nidulans*) and *Ro* (ropy in *Neurospora crassa*) gene families were first identified based on mutations leading to nuclear distribution defects and identified as components of the microtubule minus end–directed motor complex dynein as well as its accessory factor dynactin. Prime evidence for the direct connection of KASH proteins to molecular motors has just emerged. In *C. elegans*, UNC-83 interacts directly with the kinesin1 light chain KLC-2 (Fig. 5 B). Accordingly, KLC-2 as well as UNC-116 (encoding the kinesin 1 heavy chain) mutants both induce nuclear migration defects similar to UNC-83 mutants (Meyerzon et al., 2009). ZYG-12 also directly
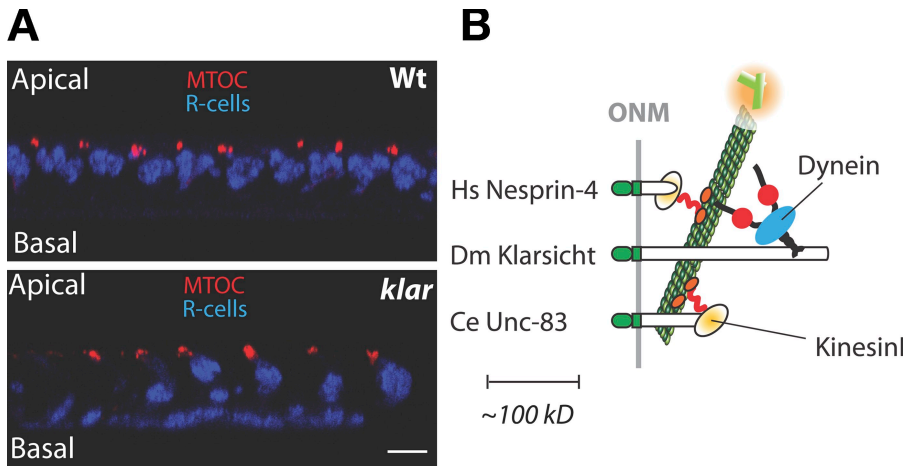
Figure 5. **KASH domain-containing proteins mediate nuclear migration.** (A, top) Cross section of wild-type *D. melanogaster* eye discs showing the apical location of photoreceptor nuclei (blue) underneath the MTOC (red). (A, bottom) Cross section of *klar* mutant eye discs showing the failure of most nuclei to migrate apically. The image is reproduced with permission from Patterson et al. (2004). Bar, ~10 µm. (B) Schematic depiction of the involvement of KASH proteins from different species in nuclear migration through their connection to the microtubule network via molecular motors.

interacts with the dynein light intermediate chain DLI-1, and, surprisingly, this interaction is essential for nuclear anchoring in the germline (Zhou et al., 2009). Nesprin-4, a newly described mammalian KASH protein, directly interacts with the light chain of kinesin 1 (Fig. 5 B). Nesprin-4 expression is restricted to secretory epithelia where microtubules are organized in lateral bundles with plus ends pointing basally. Nesprin-4 ectopic expression recruits kinesin-1 at the NE and leads to a dramatic increase in NE–centrosome distance. The Nesprin-4–kinesin-1 interaction is therefore likely to be involved in the microtubule-dependent maintenance of a basal nuclear location within secretory epithelia (Roux et al., 2009). The Kif3B subunit of kinesin II was also reported to bind directly to a fragment of Nesprin-1 containing two spectrin repeats, but the physiological relevance of that interaction still remains to be established (Fan and Beck, 2004). In the developing *Drosophila* eye, nuclear migration defects similar to Klarsicht mutants are also observed in *glued* mutants encoding dynactin (Fan and Ready, 1997; Whited et al., 2004), which suggests the involvement of dynein in the apical migration of R cell nuclei (Fig. 4, A and B). The binding of dynein and/or dynactin to mammalian Nesprins remains to be investigated.

Nucleus–centrosome coupling. From the zygote stage to the early steps of *C. elegans* embryogenesis, ZYG-12 mediates the essential attachment between the nucleus and the centrosome (Malone et al., 2003). ZYG-12 is a KASH domain–containing protein (Fig. 3, A and B) whose cytoplasmic region bears resemblance to mammalian Hook proteins (Walenta et al., 2001).

Specific ZYG-12 isoforms are recruited at the NE by SUN-1/MTF-1, and mutations of either one disrupts the coupling of the centrosome with the nucleus (Malone et al., 2003; Tzur et al., 2006a; Penkner et al., 2007). The exact nature of ZYG-12 interaction with the centrosome remains unknown (Fig. 6). Curiously, identical mutations of ZYG-12 do not alter the coupling of the centrosome to the NE in the germline (Zhou et al., 2009), which suggests the existence of alternative centrosome-tethering mechanisms.

Tethering the microtubule-organizing center (MTOC) to the yeast nucleus also involves LINC complexes. In *S. pombe*, the interaction between Sad1 and KASH proteins Kms1 and 2 (Fig. 3 B) provides a physical connection between the SPB and centromeric chromatin. The coupling of Sad1 to centromeric chromatin requires the INM protein Ima1 and the centromeric Ndc80 complex (Fig. 6; King et al., 2008). In *S. cerevisiae*, the SPB is embedded in the NE and in close contact with a membrane substructure called the half bridge (Jaspersen et al., 2006). Mps3, which localizes to the half bridge, is a SUN protein (Fig. 2 B) that interacts with Mps2 within the periplasmic space (Muñoz-Centeno et al., 1999). That interaction tethers the SPB to the half-bridge and is essential for the formation of an intact SPB (Jaspersen et al., 2006). Mps2, however, does not contain any recognizable KASH domain. Interestingly, mouse embryonic fibroblasts lacking A-type lamins or expressing disease-causing mutations thereof display migration defects, an increased distance between nucleus and centrosome, and a failure of the centrosome to polarize (Lee et al., 2007; Hale et al., 2008). Increased nucleus–centrosome
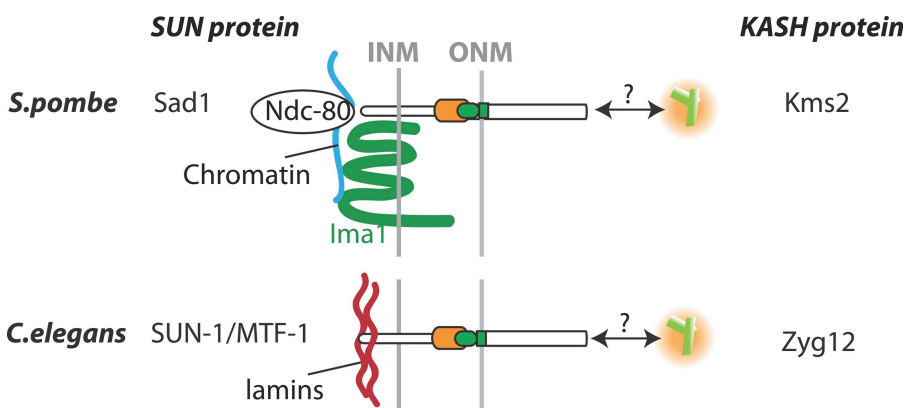
Figure 6. **SUN and KASH proteins involved in nucleus–MTOC coupling.** In *S. pombe*, the MTOC is physically coupled to centromeres (blue). That physical coupling is provided by the interaction between Sad1 and Kms2, whereas the association of Sad1 with centromeres is promoted by the centromeric Ndc80 complex and Ima1, a multispan transmembrane protein of the INM. Similarly, during *C. elegans* embryogenesis, Zyg-12 and SUN-1/MTF-1 act in concert to maintain the centrosome in close proximity to the NE. Genetic ablation of either protein severely disrupts that attachment. In both cases, the nature of the interaction between the KASH domain protein and the MTOC is not known.

distance was also observed upon LINC complex disruption in mammalian cells (our unpublished data). Collectively, these results suggest an evolutionarily conserved role for LINC complexes to position the MTOC in close proximity to the NE.

Chromosome dynamics. The "chromosomal bouquet" (Scherthan, 2001) refers to the "floral" arrangement of chromosomes during prophase I after the convergence of telomeres to a restricted area of the NE facing the centrosome (Fig. 1). SUN and KASH proteins play a central role in that dynamic event (Table I). In *S. pombe*, Sad1 colocalizes with the telomeric bouquet and interacts with meiotic-specific Bouquet (Bqt) 1 and 2 proteins to provide a physical connection between the nucleoplasmic region of Sad1 and telomeres (Chikashige et al., 2006). Because Kms1 interacts with both Sad1 and dynein (Miki et al., 2004), a model therefore emerges where telomere dynamics during bouquet formation are mediated through the Bqt2–Bqt1–Sad1–Kms1–dynein connection across the meiotic NE (Chikashige et al., 2006).

In *S. cerevisiae*, the truncation of the N-terminal region of either Mps3 or Ndj1 reduces telomere mobility of pachytene chromosomes. Ndj1 interacts with the cytoplasmic domain of Mps3 and mediates telomere attachment to the NE (Conrad et al., 2008). In conjunction with Sir4 (silent information regulator protein 4), Mps3 is also required for telomere anchoring at the NE during mitosis (Bupp et al., 2007). It is important to note that telomere dynamics are essentially mediated by actin in *S. cerevisiae*, whereas microtubules are used in mammals, plants, and fission yeast (Koszul et al., 2008).

Mammalian Sun1 clearly colocalizes with telomeres between leptotene and diplotene stages (Ding et al., 2007). Although a similar localization was reported for Sun2 in mouse and rat spermatocytes (Schmitt et al., 2007), another group was unable to detect any Sun2 immunoreactivity at meiotic telomeres (Ding et al., 2007; Lei et al., 2009). In *Sun1*$^{-/-}$ mice, telomere association with the NE as well as homologue pairing and synapsis are prevented (Ding et al., 2007). Accordingly, *Sun1*$^{-/-}$ mice are sterile, whereas *Sun2*$^{-/-}$ mice do not display any fertility issues (Lei et al., 2009). In *C. elegans*, a single point mutation within the SUN domain of SUN-1/MTF-1 (G311V) is also associated with defective homologous pairing (Penkner et al., 2007; Fridkin et al., 2009). These results indicate that Sun proteins are "hijacked" by accessory meiosis-specific proteins required for chromosome dynamics. A KASH protein that acts in concert with Sun1 in mammalian meiosis still awaits characterization.

LINC complexes and human diseases

Muscle pathologies. Over 200 missense mutations scattered along *LMNA* (the gene that encodes the A-type lamins: lamin A and lamin C) are associated with a variety of human diseases called laminopathies. Laminopathies involve either specific or combined pathologies of neurons, muscle, and bone tissues (Ben Yaou et al., 2005; Jacob and Garg, 2006; Worman et al., 2009). A main question in the field is how mutations of a protein expressed in most differentiated cells can lead to tissue-specific diseases (Mounkes et al., 2003; Worman and Courvalin, 2004). However, even though *LMNA* mutations are associated with >10 distinct human pathologies, the vast majority are associated with skeletal and/or cardiac muscle pathologies such as Emery-Dreifuss

muscular dystrophy and dilated cardiomyopathy. Two hypotheses, which are probably not mutually exclusive, view *LMNA* mutations as triggers of either gene expression deregulation or structural cellular disorganization. We will focus on the second hypothesis and emphasize the evidence for an involvement of the disruption of LINC complexes in myolaminopathies.

LMNA$^{-/-}$ mice display normal embryonic development; however, at 3 wk after birth, a decline in growth is accompanied by cardiac and skeletal myopathies reminiscent of human Emery-Dreifuss muscular dystrophy and dilated cardiomyopathy (Sullivan et al., 1999). A reduction of axon density and the presence of nonmyelinated axons resembling human peripheral axonopathies are also significant (De Sandre-Giovannoli et al., 2002). These mice die at ∼6 wk. At the cellular level, embryonic fibroblasts from *LMNA*$^{-/-}$ mice (MEF$^{lmna-/-}$) display an irregular nuclear shape and a loss of peripheral chromatin.

In MEF$^{lmna-/-}$ cells, Sun2, Nesprin-1, and Nesprin-2 all mislocalize from the NE to the ER, whereas Sun1 seems unaffected (Libotte et al., 2005; Crisp et al., 2006; Haque et al., 2006). In vivo, Sun2 and Nesprin-1 also mislocalize from synaptic nuclei of *LMNA*$^{-/-}$ and *LMNA*$^{H222P/H222P}$ knock-in mice (Méjat et al., 2009); the latter model presents muscle and cardiac phenotypes similar to Emery-Dreifuss muscular dystrophy but with a later disease onset than *LMNA*$^{-/-}$ mice (Arimura et al., 2005). In both models, anchorage of synaptic nuclei under the array of AchR is lost, phrenic nerves are highly ramified, and the innervation area is enlarged. These phenotypes are remarkably similar to *Syne-1*$^{-/-}$ mice (see Nuclear anchorage section). This indicates that (1) A-type lamins are essential for the integrity of LINC complexes in mammalian tissues and (2) A-type lamin alterations phenocopy the disruption of LINC complexes in terms of nuclear positioning and innervation pattern. However, synaptic nuclear mispositioning might not be involved in muscle pathology per se. First, dominant-negative Syne mice, *Syne-1*$^{-/-}$ mice, and *Sun1; Sun2* double knockout mice expressing Sun1 in the nervous system do not display any muscle pathology despite extensive synaptic nuclei mispositioning (Grady et al., 2005; Zhang et al., 2007b; Lei et al., 2009). Second, patients affected by autosomal recessive cerebellar ataxia associated with mutations of Nesprin-1 do not display any muscle pathology despite a severe mispositioning of synaptic nuclei in skeletal muscle (Gros-Louis et al., 2007). A major phenotypic difference, however, is that *Syne-1*$^{-/-}$ mice, *Sun1; Sun2* double knockout mice expressing Sun1 in the nervous system, and autosomal recessive cerebellar ataxia patients do not show any detectable organization defect of AchR, whereas *LMNA*$^{-/-}$ and *LMNA*$^{H222P/H222P}$ muscle fibers display poorly structured and discontinuous arrays of AchR (Méjat et al., 2009). It therefore seems that laminopathic muscle phenotypes are correlated to disorganized AchR arrays, but the question still remains as to how *LMNA* mutations alter the organization of these arrays. It is tempting to hypothesize that disruption of LINC complexes through the lack or mutation of A-type lamins alters the structural organization of the cytoskeleton. To that regard, a complete disorganization of the desmin network has been reported in *LMNA*$^{-/-}$ cardiomyocytes, and the cytoskeleton of MEF$^{lmna-/-}$ displays a drastic loss of mechanical stiffness (Broers et al., 2004; Lammerding et al., 2004; Lee et al., 2007; Hale et al., 2008). In cultured fibroblasts, disruption of LINC complexes induces a similar

loss of cytoskeletal mechanical stiffness (Stewart-Hutchinson et al., 2008). In the syncytial *C. elegans* gonad, a mutation of ZYG-12 (Q44P, *zyg-12(ct350)*) that results in the failure to recruit dynein to the NE has far-reaching deleterious effects on microtubule organization, membrane architecture, and nuclear positioning throughout the whole gonad (Zhou et al., 2009). In agreement with the concept of mechanotransduction at a distance (Wang et al., 2009), these observations support the finding that alteration of either the nuclear lamina or LINC complexes drastically affects cellular biomechanical properties of the cytoskeleton. HL-60–derived granulocytes may provide a physiological adaptation of that phenomenon. The cytoskeletal malleability and extensive nuclear lobulation that allow these cells to cross the vasculature has been correlated to the expression of a paucity of LINC complex components, whereas the stiffer macrophage-derived cells express most of the LINC complex components (Olins et al., 2009).

A-type lamin mutations affecting the structural integrity of LINC complexes may therefore compromise the organization and mechanical integrity of the myoskeleton. Because AChR arrays are primarily supported by a submembranous organization of actin and desmin filaments (Mitsui et al., 2000), a major cytoskeletal disruption caused by a mutation of the nuclear lamina could therefore drastically impact the organization of these receptors. Finally, Nesprins and dystrophins are giant spectrin-repeat proteins with actin-binding domains that mechanically connect to proteinaceous meshworks—nuclear lamina or extracellular matrix—through KASH domains or via the sarcoglycan–dystroglycan complex, respectively. Accordingly, cultured myotubes from dystrophin-deficient Mdx mice are mechanically compromised (Pasternak et al., 1995). Collectively, these observations suggest that laminopathic mutations affecting the organization of LINC complexes may induce significant mechanical deficiency and ensuing structural disorganization of the muscle fiber.

Several indications also support the direct involvement of mutations of LINC complex components in muscle pathologies. First, *D. melanogaster* Msp-300 was initially shown to be required for embryonic muscle morphogenesis (Rosenberg-Hasson et al., 1996), and Nesprin immunoreactivity was also detected in sarcomeres and Z lines, which supports additional structural roles for Nesprins (Zhang et al., 2005). Second, another mouse model with the homozygous deletion of the KASH domain of Syne-1 (Δ/Δ KASH model) displays ~50% perinatal lethality, and survivors exhibit Emery-Dreifuss muscular dystrophy phenotypes (Puckelwartz et al., 2009). This striking difference with the *Syne-1*$^{-/-}$ model may stem from either a dominant-negative effect of truncated Syne-1 proteins detected in Δ/Δ KASH mice or from different genetic backgrounds. Third, Nesprin missense mutations have recently been identified in Emery-Dreifuss muscular dystrophy patients (Zhang et al., 2007a) and in autosomal recessive arthrogryposis multiplex congenita of myogenic origin (Attali et al., 2009). These observations, in addition to the lack of molecular diagnoses in >50% of Emery-Dreifuss muscular dystrophy phenotypes, stress the need to screen patients with idiopathic muscular dystrophies for mutations of *Nesprin* and *Sun* genes.

Neuronal diseases. Because SUN and KASH domain–containing proteins are involved in nuclear migration, they may be required in essential developmental processes relying on nucleokinesis, i.e., the translocation of the nucleus within a cell, and may underlie other categories of human diseases. In filamentous fungi, NudF and ro-15 are essential for nuclear positioning and encode proteins with 40% identity to human LIS1 (Morris et al., 1998). Deletion or mutations of LIS1 are associated with lissencephalies, pathologies of the developing brain that are associated with a failure of the nucleokinetic step during neuronal migration in the cortex (Solecki et al., 2004; Vallee and Tsai, 2006). In cerebellar granule neurons, nucleokinesis requires intact microtubules that literally wrap the nucleus (Rivas and Hatten, 1995; Solecki et al., 2004) and a functional dynein–dynactin complex as well as Lis1 (Tanaka et al., 2004) and Ndel1, one of its binding partners (Shu et al., 2004). Current models suggest that dynein, anchored at the NE, pulls the nucleus toward the minus end of microtubules (Samuels and Tsai, 2004; Tsai and Gleeson, 2005). How the microtubule network is physically connected to the neuronal NE remains a central question (Tsai and Gleeson, 2005). However, as we have seen, LINC complexes are involved in nuclear migration, and the recent demonstration that UNC-83 and Nesprin-4 both interact with molecular motors strongly predicts a central involvement of LINC complexes in neuronal migration. In that regard, either the mutation of *mikre oko* (*mok*), which encodes a subunit of the dynactin complex, or interference with the function of dynamitin, LIS1, or LINC complexes results in the mislocalization of zebrafish photoreceptor nuclei (Tsujikawa et al., 2007). The discovery of Syne-1 mutations in patients with autosomal recessive cerebellar ataxia (Gros-Louis et al., 2007) could be the first description of the involvement of Nesprins in neurological diseases.

Finally, interkinetic nuclear migration designates the coupling of nuclear migration with the cell cycle of neuroepithelial cells. This phenomenon is essential for regulation of cell cycle exit and neurogenesis (Baye and Link, 2008). The down-regulation of Syne-2 or the expression of its KASH domain alters interkinetic nuclear migration (Del Bene et al., 2008). Together, these results predict exciting times ahead for LINC complexes in nuclear migration and neurogenesis not only during development but also in the adult brain, where focal neurogenesis and nuclear migration are still significant (Ming and Song, 2005; Ayala et al., 2007).

Conclusion

The past decade has seen remarkable progress in our understanding of the functional contribution of NE proteins to essential biological processes. Such progress largely benefited from multidisciplinary approaches in different organisms. The accumulated data clearly established that SUN proteins act as NE "receptors" of KASH domain-containing proteins. The variety of cytoplasmic "flavors" of KASH proteins, in turn, provides specific functions related to nuclear and chromosome dynamics. However, many questions still remain. For example, how the SUN–KASH interaction is regulated is only beginning to emerge, with early indications pointing to TorsinA, an AAA+ATPase (Nery et al., 2008; Vander Heyden et al., 2009). The interaction network of the nucleoplasmic region of Sun proteins also needs more investigation in interphase cells. We have seen that gigantic macromolecular complexes form both within the nucleoplasm and the cytoplasm around LINC complexes, but how cell signaling affects

these assemblies is still poorly characterized. Hypotheses on how these molecular assemblies might affect mechanochemical conversion in the nucleus and alter gene activities have recently begun to emerge (Wang et al., 2009). Molecular tools are now available to ask essential questions about the physiological significance of nuclear positioning in other tissues. From a disease standpoint, examining the role of SUN–KASH interactions in neuronal migration will also be essential for establishing whether these interactions participate in the etiology of lissencephaly-like phenotypes. Finally, accumulated evidence calls for mutation screenings of Sun proteins and Nesprins in patients affected by idiopathic muscular dystrophies. Such findings could provide new therapeutic insights into these devastating human pathologies.

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