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LINC complex proteins in cardiac structure, function, and disease

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Abstract

The LINC (LInker of Nucleoskeleton and Cytoskeleton) complex, composed of proteins within the inner and the outer nuclear membranes, connects the nuclear lamina to the cytoskeleton. The importance of this complex has been highlighted by the discovery of mutations in genes encoding LINC complex proteins, which are causative for skeletal or cardiac myopathies. Herein, this review summarizes structure, function, and interactions of major components of the LINC complex, highlights how mutations in these proteins may lead to cardiac disease, and outlines future challenges in the field.

Keywords

Nucleus; Cardiac Myocyte; Cardiomyopathy

Introduction

The division between cytoplasm and nucleus is defined by the nuclear envelope (NE), which consists of two lipid bilayers, the inner and the outer nuclear membranes (INM and ONM respectively) (Fig.1). The lumen between the two layers is known as the perinuclear space (PNS). The INM and ONM are fused periodically at nuclear pore complexes (NPCs) that regulate bidirectional macromolecular trafficking across the NE[1–3] (Fig.1). Immediately underlying the INM is the nuclear lamina, a meshwork of intermediate filaments composed of A- and B-type Lamins, which play a critical role in providing structural integrity to the NE, as well as providing anchoring sites for chromatin domains and regulatory proteins, including signaling molecules and transcription factors[4]. Proteins within the INM and ONM act as a LInker of the Nucleoskeleton and Cytoskeleton, termed the LINC complex[5, 6] (Fig. 1).

The LINC complex provides structural support to the nucleus and physically couples the nucleoskeleton with the cytoskeleton[7–11]. This NE-spanning supramolecular chain may serve as a mechanosensor, translating mechanical cues, which include physical forces (e.g.,

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tension, compression or shear stress) and alterations in extracellular matrix (ECM) mechanics, into biochemical signals, thus allowing cells to adapt to their physical environment[12, 13]. By mediating changes in cytoskeletal and nuclear organization/structure/positioning, these mechanical signals may also influence chromatin localization and organization, and thereby modulate gene expression by altering interactions with active transcription complexes, or by altering intracellular signaling pathways [12–16].

A wide range of cardiac and skeletal myopathies have been linked to mutations in LINC complex proteins. These diseases include, but are not limited to, dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (AC), and Emery-Dreifuss muscular dystrophy (EDMD)[17–21]. In this review, we discuss the structure, function, and interactions of major components of the LINC complex, including Nesprins, Sun proteins, Emerin, and Luma, and associated Lamins, and highlight how mutations in these proteins may lead to cardiac disease.

Nesprins

The ONM components of LINC complexes are made up of a four-member family of spectrin-repeat (SR) transmembrane proteins termed NE spectrin-repeat proteins (Nesprins)[22, 23]. The founding member of this protein family, Nesprin 1, was alternatively named synaptic NE-1 (Syne-1)[24], Enaptin[25], or myocyte NE protein-1 (Myne-1)[26] due to its simultaneous discovery by a number of independent groups. Nesprin 1 was first discovered during a search for specific gene markers of contractile differentiated vascular smooth muscle cells (VSMCs). In a differential expression screen of differentiated versus dedifferentiated VSMCs, a cDNA clone (1RA1) was identified that was more strongly expressed in differentiated VSMCs[27]. Isolation and full length sequencing of the human ortholog of 1RA1 identified a gene encoding a protein (hereafter referred to as Nesprin 1), which localized to the NE in C2C12 myoblasts and human VSMCs[28]. Nesprin 1 was also found to be highly expressed in nuclei that lie beneath the postsynaptic membrane at the neuromuscular junction of adult skeletal muscle fibers[24], and at the NE of smooth, skeletal, and cardiac muscle[26]. The expression pattern of mammalian Nesprin 1 therefore implies a specific role in muscle function, further suggested by its abundance in the sarcomeric Z-line of both human skeletal and cardiac muscle[22].

Sharing >60% homology with Nesprin 1, Nesprin 2 was discovered simultaneously in both a differential cDNA screen[28], and a yeast two-hybrid screen used to identify proteins concentrated in the postsynaptic membrane[24]. Accordingly, Nesprin 2 is otherwise known as Syne-2, or nucleus and actin connecting element (NUANCE), having been identified as a novel protein during a database search using the peptide sequence of the actin-binding domain (ABD) of known α-actinin-related proteins[29]. Nesprin 2 was found to be predominantly expressed at the ONM and in the nucleoplasm of multiple cell types[29], a rather uncharacteristic feature of actin-binding proteins.

Multiple Nesprin isoforms that vary markedly in size are produced by alternative transcriptional initiation, RNA splicing, and termination of the two independent Nesprin 1 and Nesprin 2 genes[23, 30 31]. Giant isoform Nesprin 2 (Nesprin 2G) was first cloned by

combining Rapid Amplification cDNA Ends (RACE)-PCR with the analysis of data available from human EST and genomic databases[29]. Independently, Zhang et al. performed bioinformatic examination of the genomic regions of human Nesprin 1 and 2 and predicted the existence of giant isoforms, Nesprin 1G and Nesprin 2G, with calculated molecular weights of 1.01 MDa and 796 kDa, respectively[22, 28]. Nesprin 1G cDNA was later cloned with mRNA extracted from mouse brain[25]. Both Nesprin 1G and Nesprin 2G consist of an N-terminal tandem repeat of calponin-homology (CH) domains, an SR-containing rod domain, and a C-terminal transmembrane Klarsicht, ANC-1, and Syne Homology (KASH)-domain. The two giant proteins bind to the actin cytoskeleton via their CH domains, whereas the C-terminal transmembrane KASH domains mediate their localization and stabilization at the NE by interacting directly with Sad1/UNC-84 or SUN-domain containing proteins residing in the INM[5, 7–9, 25, 29, 32]. The existence of these giant isoforms in striated muscle has yet to be confirmed by western blot and/or cDNA data.

The smaller Nesprin 1 and 2 isoforms that have been documented include, but are not limited to, Nesprin 1α, Nesprin 1β, Nesprin 2α, Nesprin 2β, and Nesprin 2γ[24, 28]. For a detailed review and schematic representations of the various Nesprin isoforms we refer readers to recent publications [31, 33]. In comparison to their respective giant isoforms, the short isoforms either lack the N-terminal CH domains and/or the C-terminal KASH domain, or vary in the length of their SR-containing rod domains[34]. For example, the Nesprin 1α isoform contains the KASH domain and SRs, but lacks the CH domains[24, 26, 28]. Nesprin 1α localizes to the NE and has been reported to interact with itself, Emerin and Lamin A/C[26, 35]. Like Nesprin 1α, Nesprin 2α is expressed predominantly in heart and skeletal muscle, as detected by northern blot and RT-PCR analysis[28, 32], and co-localizes with Emerin and Lamin A/C in the NE of VSMCs[32]. Whilst direct interactions between Nesprin 1α, Nesprin 2α, Emerin, and Lamin A/C have been reported, the recently solved crystal structure of SUN domains interacting with KASH peptides of Nesprins implies that KASH-containing Nesprin isoforms reside in the ONM[9]. As Nesprins are a multi-isoform protein family, many antibodies have been generated against different regions/domains of each protein isoform. It should be duly noted however, that the specificities of many of the antibodies described have to date not been thoroughly validated in suitable Nesprin knock-out animal models. Furthermore, the lack of isoform specific sequences in many of the Nesprin variants makes it difficult to design antibodies targeting a single isoform[33].

Recent data suggest that missense mutations in Nesprin 1 and 2 may be involved in the pathogenesis of EDMD-like phenotypes, including cardiomyopathy[36, 37]. Screening for DNA variations in genes encoding Nesprin 1 and 2 was performed on 190 EDMD or EDMD-like patients lacking Lamin or Emerin mutations. Four heterozygous missense mutations were identified (R257H, V572L and E646K in Nesprin 1α and T89M in Nesprin 2β), which occurred at positions that are highly conserved evolutionarily and which lie within the Lamin and Emerin binding domains of Nesprin 1 and 2[36]. Fibroblasts from these patients exhibited nuclear morphological defects, and mislocalization of Emerin and SUN2. These observations could be recapitulated by siRNA knockdown of Nesprin 1 or 2 in normal fibroblasts. In addition, diminished NE localization of Nesprins and impaired Nesprin/Emerin/Lamin binding interactions were common features of all EDMD patient fibroblasts. These results suggest that defective LINC complexes and uncoupling of the nucleoskeleton

and cytoskeleton may play a significant role in the muscle-specific pathogenesis of EDMD[36, 38].

In an independent study, a patient with the R374H missense variant in Nesprin 1α, but no mutations in *LMNA*, was identified in a screen of 46 unrelated patients with non-ischemic cardiomyopathy[37]. This individual developed severe DCM and required cardiac transplantation at 26 years of age. Patient-derived fibroblasts displayed increased expression of LINC complex proteins Nesprin 1α and Lamins A and C. Due to the association of Nesprin 1 mutations with cardiac disease, Puckelwartz and colleagues also characterized the cardiac phenotype of a mutant mouse model in which the KASH domain of Nesprin 1 was specifically replaced by a stretch of 61 unrelated C-terminal amino acids (Nesprin1^{rKASH})[39]. Homozygous mutant mice exhibited lethality, with approximately half dying at or near birth from respiratory failure. Surviving mice displayed progressive muscle weakness, a characteristic of EDMD, and with increasing age developed cardiomyopathy with associated cardiac conduction defects[37, 39]. Absence of the KASH domain prevented Nesprin 1 from binding to SUN proteins, thereby disrupting the LINC complex[39, 40]. Furthermore, cardiomyocyte nuclei were found to be elongated with reduced heterochromatin in Nesprin1^{rKASH} hearts[39]. These findings mirror what has been described for Lamin A/C mutations and reinforce the importance of an intact LINC complex for normal cardiac function[41]. Of note however, is the observation that in this model, mutant Nesprin 1α protein was similar in size (120 kDa), owing to the replacement of 100 amino acids of the KASH domain with an alternate 61 amino acids, and was produced at the same level as wild-type Nesprin 1α in skeletal muscle samples[39]. It is unclear from the data presented as to whether other mutant Nesprin 1 isoforms were present, since no proteins with molecular weights above 120 kDa were shown by western blot analysis[39].

In other mouse models, ablation of the KASH domain of either Nesprin 1 (Nesprin1$^{\Delta KASH}$) or Nesprin 2 (Nesprin2$^{\Delta KASH}$) has been reported to have no effect on either viability or fertility; however, double mutants die of respiratory failure within 20 minutes of birth[42]. Nesprin 1α is highly expressed in synaptic nuclei of syncytial muscle fibers and is upregulated during myotube differentiation[24, 26, 28]. In Nesprin 1$^{\Delta KASH}$ mutants, clusters of synaptic nuclei are abolished and mice display abnormal positioning of non-synaptic nuclei in skeletal muscle[42]. Heart and muscle function of these mice has not been reported. In the absence of western blot analysis however, it is unclear whether truncated mutant proteins lacking the KASH domain or native Nesprin isoforms that lack the KASH domain are still present in these mouse models[42]. Interestingly, expression of a dominant negative form of Nesprin 1, which encodes the C-terminal KASH domain, results in mislocalization of neuromuscular junction nuclei[43]. Another group has reported that mice lacking the ABD of Nesprin 2G were viable and almost indistinguishable from wild-type mice, except for slight epidermal thickening[44]. Interestingly, fibroblasts from these mice exhibited abnormal nuclear morphology and an uneven distribution of Emerin in the NE.

The two Nesprin 1 mutant mouse lines discussed above were generated by either partially removing[42] or completely replacing[39] the last exon of Nesprin 1, which encodes the KASH domain. Since KASH-less Nesprin 1 isoforms have been shown to exist, we generated Nesprin 1 mutants by targeting an exon that is shared by all Nesprin 1 isoforms containing

the C-terminal SR region with or without the KASH domain (hereafter referred to as Nesprin $1^{-/-}$ mice)[45]. Nesprin $1^{-/-}$ mice have markedly decreased survival rates, growth retardation, increased variability in body weight, and compromised exercise capacity compared with wild-type animals. In agreement with the previous studies[39, 42], we found that Nesprin 1 is critical for nuclear positioning and anchorage in skeletal muscle. Of the LINC complex-associated proteins examined, only SUN1 and SUN2 were slightly upregulated in Nesprin $1^{-/-}$ cardiac and skeletal muscle, respectively[45]. No defects in cardiac contractile function were observed in our Nesprin $1^{-/-}$ mice up to 12 months of age, although function was not tested in older mice[45]. To this end, it would be of great interest to investigate whether Nesprin 1 and 2 have distinct and overlapping roles in cardiac muscle nuclear positioning, nuclear membrane integrity, and cardiac muscle function by generating mouse lines in which Nesprin 1 and 2 are specifically ablated in developing cardiac muscle and adult cardiomyocytes. It will also be important to determine the roles of different isoforms of Nesprin 1 and 2 by generating isoform-specific knock-out mice.

Nesprin 3, Nesprin 4 and KASH5

Nesprin 3 was first identified in a proteomics screen to identify novel NE proteins and was subsequently found to interact with the ABD of human Plectin 1C using a yeast two-hybrid screen[46 47]. Nesprin 3 has two protein isoforms, 3α and β, which contain a C-terminal KASH domain but lack N-terminal CH domains[47]. The KASH domain interacts with SUN1 and SUN2 to retain Nesprin 3α at the ONM, and the N-terminus of Nesprin 3α interacts with the ABD of Plectin, which in turn interacts with intermediate filaments[47, 48]. Nesprin 3 is conserved throughout evolution and is ubiquitously expressed in mouse tissues, importantly localizing to the NE in both skeletal and cardiac myocytes[47, 49, 50]. Nesprin 3 knock-out zebrafish and mice are viable and do not display any basal phenotype[49, 50]. It would be interesting however, to investigate whether these mice have an abnormal cardiac response to stress or present an age-related phenotype, as Nesprin 3 has been found to regulate cell morphology during flow-mediated mechanical loading and cell migration in a 3D collagen matrix[51, 52].

Nesprin 4 was discovered by performing a BLASTP search for sequences similar to the KASH domain of Nesprin 2[53]. Nesprin 4 localizes to the ONM and contains a single SR domain and a C-terminal KASH domain. Nesprin 4 interacts with Kinesin-1 as shown by co-immunoprecipitation and a yeast two-hybrid screen, and recruits Kinesin-1 to the NE when expressed in heterologous HeLa cells[53]. Nesprin 4 knock-out mice appear overtly normal with no obvious loss of viability; however, they do display defects in hearing[54]. Whether Nesprin 4 is expressed in the heart remains to be determined.

KASH5 was identified by performing a yeast two-hybrid screen using a testes cDNA library and the mouse cohesin protector protein shugoshin-2 as bait[55]. KASH5 contains a C-terminal KASH domain that interacts with SUN1 and SUN2, and a central coiled-coil region. Its expression appears to be limited to the testes, and has yet to be described in the heart.

SUN proteins

Sad1/UNC-84 or SUN proteins were originally described in fission yeast (Sad1)[56] and C. elegans (UNC-84)[57]. BLAST searches using the conserved C-terminus (now termed the Sad1/UNC-84 or SUN domain) revealed the mammalian homologues, SUN1 and SUN2, which were subsequently cloned using a cDNA library from human brain[57]. Since the identification of SUN proteins in mammals, five mammalian family members (SUN1-5) have been identified[10]. Whereas SUN1 and SUN2 are ubiquitously expressed, SUN3, SUN4 (SPAG4) and SUN5 appear to be specifically expressed in the testes[58–60]. For the purposes of this review, we will focus on the roles of SUN1 and SUN2 as they have been identified in the mouse heart and skeletal muscle[5, 39, 45]. For a more extensive overview of SUN proteins in other tissues and cell types we refer readers elsewhere[61].

SUN1 and SUN2 are type II membrane proteins[62, 63]. Human SUN1 is the largest member of the SUN-domain family containing 812AAs and having a molecular mass of ~90 kDa. SUN2 contains 717AAs and a predicted molecular mass of ~80 kDa. Overall, SUN1 and SUN2 proteins show high degrees of similarity and share 64% homology[7]. SUN1 and SUN2 both have an N-terminal region localized at the nucleoplasm,[5, 7] which is abutted to a single transmembrane domain that spans the INM[6, 61]. The bulk of SUN1 and SUN2 are composed of the stalk region, which spans the PNS and is comprised of coiled-coil repeats that is thought to be essential for trimerization[9, 64, 65]. The most highly conserved region between family members is the C-terminal SUN domain, which is made up of ~175AAs and interacts with Nesprins.

To our knowledge, only the longest isoforms of SUN1 and SUN2 have been shown to be expressed in the heart at the protein level[45]. Interestingly, a recent study found 6 potential splice isoforms of SUN1 expressed in the heart using RT-PCR[66]. All predicted isoforms contain the canonical SUN domain, stalk region, and transmembrane domain, but have varying lengths that protrude into the nucleoplasm. At present, there is no experimental evidence to suggest differential splicing of SUN2[62]. It remains to be seen whether or not these isoforms are translated into protein, and if so, what distinct roles they may have.

SUN1 and SUN2 have been shown to interact directly with nuclear Lamins[5, 7]. Specifically, overexpressed HA-tagged SUN1 co-immunoprecipitates with GFP-conjugated Lamin A in U2OS cells. Furthermore, an in vitro transcribed/ translated N-terminus of SUN1 was found to interact with in vitro transcribed/ translated Lamin A, but not Lamin C, B1 or B2[7]. In another study, a GST-conjugated N-terminus of SUN1 was found to preferentially interact with in vitro transcribed/ translated pre-Lamin A over mature Lamin A, and weakly interacted with Lamins C and B1[5]. In HeLa cells, overexpression of Myc-tagged pre-Lamin A, but not Lamin B1 relocalized a HA-tagged N-terminus of SUN1 from the nucleoplasm to the NE. This interaction appears to be evolutionarily conserved, as the localization of one of the two SUN protein homologues expressed in C. elegans, UNC-84, was found to be dependent on Lamins[67]. Given the foregoing in vitro interaction and immunofluorescence data, it was somewhat surprising that in Lamin A/C-null mouse embryonic fibroblasts (MEFs), SUN1 was still able to localize to the NE. In support of this, others have shown that

SUN1 was able to localize to the NE when Lamin A/C and/or B1/ B2 were knocked down in HeLa cells[68].

Similarly to SUN1, the HA-tagged N-terminus of SUN2 could be recruited from the nucleoplasm to the NE by overexpressing Myc-tagged pre-Lamin A, but not Lamin B1 in HeLa cells[5]. In addition, in vitro pull-down assays revealed that the N-terminus of SUN2 interacts weakly with Lamins A, C and B1. In contrast to SUN1, the localization of SUN2 showed some dependence on Lamin A/C, as SUN2 was unable to localize to the NE in the majority of MEFs devoid of Lamin A/C[5].

These data clearly imply some role of nuclear Lamins in the localization of SUN proteins. However, in light of recent evidence, where *lmna*$^{-/-}$ mice were shown to produce truncated Lamin A that may be capable of interacting with SUN proteins, data using the Lamin A/C-null MEFs must be interpreted with caution[69]. The region of Lamin A that interacts with SUN1 maps to residues 389–664[7] and the truncated Lamin A produced by the 'Lamin A/C null' MEFs retains 78 of 275AAs. It is therefore possible that the remaining 78AAs could mediate the interaction between SUN1 and truncated Lamin A. In contrast, for SUN2, the 197AA of the 275AA interaction domain that are lost in the 'Lamin A/C null' MEFS may be critical for retention of SUN2 at the INM.

Whether or not Lamin-independent mechanisms exist to localize SUN1 and SUN2 to the INM remains to be seen. However, it is clear that other mechanisms exist to recruit SUN proteins to the INM. For example, in C. elegans, UNC-84 requires a combination of two nuclear localization signals (NLSs), an INM-sorting motif, and a NE-localization signal (NELS) that is evolutionarily conserved with mammalian SUN1[63]. In support of the hypothesis that other localization mechanisms exist, Turgay and colleagues demonstrated that in addition to Lamin A/C, SUN2 requires a combination of its NLS, Golgi-retrieval sequence, and the SUN domain for localization to the INM[70].

Various mechanisms have been speculated to retain SUN1 and SUN2 at the INM, including binding to the Lamins and heterochromatin[10]. Intriguingly, one study found that the N-termini of SUN1 and SUN2 were able to interact with Emerin and short isoforms of Nesprin 2 that localize to the INM[71]. Clearly, further work is required to investigate whether these interactions have functional consequences in vivo.

Whereas the localization and connection between SUN1 and SUN2 to the nucleoskeleton seem to require a combination of factors, it is clear that the connection between the cytoskeleton and SUN1 and SUN2 is directly through members of the Nesprin family[9, 64, 65]. The crystal structure of SUN2 revealed that it forms a trimer[9, 64], which is essential for coordination and recruitment of the KASH domains of Nesprin 1 and Nesprin 2[65]. Three SUN domains form a hexameric complex with three KASH peptides of the Nesprins, and coordinate them using a combination of hydrogen bonds, a "KASH lid" and disulfide bridges. The extensive covalent and non-covalent attachments as well as the binding avidity between three KASH domains with three SUN domains are thought to enable the LINC complex to transmit force between the cytoskeleton and the nucleoskeleton[61]. This is of critical importance in cardiomyocytes that are constantly

undergoing mechanical stress for both maintenance of the NE architecture as well as sensing and responding to changes in force.

Given the interaction partners and localizations of SUN1 and SUN2, they are likely candidates for playing a role in the pathogenesis of cardiomyopathy. For example, mutations in Lamin A/C that result in progeria show upregulated levels of SUN1 in patient-derived fibroblasts[72]. Interestingly, downregulation of SUN1 in mouse models for both progeric (LmnaΔ9) and dystrophic (*lmna*$^{-/-}$) laminopathies ameliorated the phenotypes observed and significantly extended the lifespan of the mice. Specifically, histological sections from *lmna*$^{-/-}$ hearts revealed an increase in sarcoplasmic vacuoles and an increase of inflammatory cells in the myocardium. These features were ameliorated in the *lmna*$^{-/-}$ *SUN1*$^{-/-}$ double knock-out (DKO) mice. In addition, the cardiac function as measured by ejection fraction was restored to near wild-type levels of ~70% in the *lmna*$^{-/-}$ *SUN1*$^{-/-}$ DKO compared to ~50% in *lmna*$^{-/-}$ mice. Intriguingly, SUN1 accumulated in the Golgi of *lmna*$^{-/-}$ and LmnaΔ9 MEFs, which resulted in cytotoxicity. However, the underlying molecular mechanisms behind the pathogenesis remain unknown.

Interestingly, one study in mice using a global knock-out approach to ablate SUN1 and SUN2 expression in all tissues resulted in perinatal lethality[73]. While the causes of death were not ascertained in great detail, it appears that the lungs were not fully inflated in the DKO. Interestingly, the DKO was rescued by expressing SUN1 using a transgenic approach under a neuron-specific promoter. Also, it is intriguing that this phenotype is similar to that of Nesprin 1 and Nesprin 2 double global knock-out mice.

Another potential association between SUN1 and SUN2 and disease is through a mutation in Emerin that results in X-linked EDMD[74]. It has been shown that the disease causing mutation in Emerin reduces the strength of binding between Emerin and SUN1 or SUN2[71].

Despite these data, the precise role of SUN1 and SUN2 in the heart remains elusive. Clearly studies in cardiac specific knock-out mouse models will further our understanding of these key factors.

Emerin

The gene coding for Emerin was first identified in 1994 by genetic mapping of X-linked recessive EDMD[74]. Emerin is a type-II integral membrane protein, which contains a nucleoplasmic N-terminal domain, followed by a single transmembrane region that spans the INM, and a short luminal tail that resides in the PNS[75, 76]. Emerin is ubiquitously expressed in tissues and predominantly localizes to the NE in skeletal and cardiac muscle where it is thought to be retained at the INM via its interaction with A-type Lamins[75–79]. Emerin has multiple binding partners, including but not limited to SUN1, SUN2, Nesprin 1α, and the chromatin-interacting protein, barrier to auto-integration factor (BAF), which provides a link between Emerin and chromatin[35, 71, 80]. For a comprehensive list of binding partners and their interaction regions we refer readers to a recent review[81].

Mutations in Emerin cause X-linked EDMD, lead to cardiac conduction defects and DCM, as well as defects in skeletal muscle[74, 75, 82–85]. The number of disease causing mutations in

Emerin is vast and we refer readers elsewhere for a comprehensive overview[86, 87]. Many of the Emerin disease-causing mutations lead to its depletion in cells[75, 76]. It is therefore surprising that Emerin knock-out mice have been reported to either display a very mild age-related atrioventricular conduction defect or no overt skeletal or cardiac phenotype[88, 89].

Interestingly, Emerin-deficient MEFs have abnormal nuclear shape[88], altered NE elasticity[90] and display an impaired response to mechanical stimulation as measured by expression levels of mechanosensitive genes *iex-1* and *egr-1*[88]. After sustained mechanical strain, the number of apoptotic cells is higher in Emerin-null MEFs compared to wild-type cells[88]. It was therefore postulated that Emerin might play a role in mechanosensing and regulate expression of genes to enable the cell to adapt to mechanical load. In support of this, a recent report suggests that Emerin indirectly regulates the localization and therefore signaling of the mechanosensitive transcription factor megakaryoblastic leukaemia 1 (MKL1) [91] by modulating actin dynamics. MKL1 is a co-activator of serum response factor (SRF), which is a master regulator of genes encoding numerous cytoskeletal proteins, including both Vinculin and Actin.

Whilst it is clear that mutations in Emerin are the unequivocal cause of X-linked EDMD, studies with cardiomyocytes derived from human EDMD patient-derived induced pluripotent stem cells (iPSCs) may reveal the molecular basis behind the disease.

Luma

Luma (*TMEM43*) was first identified in a proteomics screen for new INM proteins in neuroblastoma cells and was subsequently cloned and shown to localize to the NE in COS-7 cells[46, 92]. Luma is widely expressed in human tissues, and importantly has been shown to be expressed in the heart[93, 94]. Interestingly, Luma is highly conserved throughout metazoans and is also expressed in insects, and unicellular eukaryotes implying that it plays an essential, non-redundant role in cells. Luma contains four transmembrane (TM) domains that are thought to play a role in self-oligomerization[93, 95]. The majority of the protein resides in the PNS and comprises a large hydrophilic domain that is located between TM1 and TM2. Luma has been shown to interact with Lamins A/C, B1, Emerin, and SUN2[93, 95], and may play a role in regulating Emerin localization.

Luma has been identified as the unequivocal cause of arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5)[94, 96, 97]. The mutation in Luma causing ARVC5 changes residue Serine 358 to Leucine residue (S358L) in the third TM domain[96]. The ARVC5 locus was mapped in an extended eight-generation family from the genetically isolated population of the Canadian island of Newfoundland. ARVC5 is a lethal, fully penetrant, sex-influenced, autosomal dominant disorder. Typically, it affects males more than females as affected men have a median lifespan of 41 compared to 83 in the control group, whereas affected women have a median lifespan of 71. The disorder is fully penetrant by the age of 63 and 76 in men and women, respectively. The most prominent clinical features of ARVC5 were premature ventricular contractions (PVCs) and left ventricular dilatation, resulting in heart failure and sudden cardiac death. Interestingly, another study identified two EDMD patients in which two novel mutations in Luma were found, E85K and I91V[95]. Unfortunately, the patient with

the E85K mutation died after a muscle biopsy was taken, and the patient's son who reportedly had the same phenotype was lost to follow-up. Therefore no mutation analysis or segregation studies could be performed. For the I97V patient, her parents died with no mention of any specific causes, and she did not have any children. Therefore, unlike the S358L mutation that is genetically traceable, the E85K and I91V mutations can only be associated with EDMD and it remains to be seen whether they are causative factors in EDMD.

The underlying molecular mechanism(s) behind the pathogenesis of ARVC5 caused by the S358L mutation in Luma remains to be elucidated. However, Luma was identified as a potential target gene of the adipogenic transcription factor, PPARγ[98], indicating a potential link between the fibrofatty replacement of cardiomyocytes in the hearts of ARVC5 patients. Clearly, further work using mouse models and patient-derived iPSCs are needed to reveal the molecular function of Luma in cardiac function and disease.

Nuclear Lamins

Nuclear Lamins were first described in 1978[99]. Nuclear Lamins are type V intermediate filaments, which readily self-associate to form parallel coiled-coil homodimers. These homodimers are then able to form higher-order filamentous structures to form the nuclear lamina, situated beneath the INM. The main components of the nuclear lamina are the A-type and B-type nuclear Lamins, which share a common overall structure, comprising of a central α-helical rod, which is flanked by non-helical, globular domains at either terminus[100].

The A-type Lamins are encoded by a single gene, *LMNA*, that is alternatively spliced to generate the major Lamins, A and C, as well as the minor Lamins, AΔ10 and C2[101, 102]. The expression of A-type Lamins is ubiquitous and is developmentally regulated, as their expression is only detected in differentiated cells[103]. In contrast, B-type Lamins are constitutively expressed and are found in many tissues[104]. The B-type Lamins, Lamin B1 and B2, are encoded by *LMNB1* and *LMNB2*, respectively[105, 106]. For a comprehensive overview of the discovery and description of nuclear Lamins, we refer the readers to another review[107].

Mutations in *LMNA* cause a broad range of human diseases, collectively known as 'laminopathies'[108, 109]. Laminopathies are comprised of more than a dozen previously defined clinical disorders and include several forms of muscular dystrophies, such as autosomal dominant (AD)-EDMD[110], limb-girdle muscular dystrophy[111], DCM[112], heart-hand syndrome[113], and a newly discovered LMNA-related congenital muscular dystrophy or L-CMD[114]. The myriad of diseases caused by mutations in the gene coding for Lamin A/C surpasses any other known gene[115] and are beyond the scope of this review. For an overview of the laminopathies that result in cardiac diseases, we refer readers elsewhere[116].

The many roles of Lamins are mediated by interactions with numerous Lamin-binding proteins both at the nuclear periphery and in the nucleoplasm[117]. In addition to providing structural integrity to the NE, playing a role in cytoskeletal organization and nuclear positioning, there is also growing evidence that Lamins regulate chromatin organization and

gene expression, and influence cell signaling[118–123]. Lamins can interact with chromatin either directly or through histones and other INM and non-integral membrane proteins, such as Lamin B receptor (LBR), heterochromatin protein 1 (HP1), Emerin, and BAF[4, 124–126] (Fig. 1).

As substantial data support a role for Lamin A/C in its interaction with chromatin and gene regulation[15], Mewborn and colleagues examined gene expression changes in hearts and fibroblasts resulting from a dominant *LMNA* mutation, E161K, associated with inherited cardiomyopathy[127, 128], and correlated this with changes in chromosome positioning[129]. As well as having a high percentage of misexpressed genes, chromosome 13 was found to be less tightly associated with the nuclear membrane in *LMNA* E161K mutant cells, and the entire chromosome territory was displaced to a more intranuclear position compared to control cells[129], thereby linking abnormal gene expression and intranuclear position. Gross mislocalization of chromosome 13 was also observed in another fibroblast line with a *LMNA* gene mutation, D596N, associated with both cardiomyopathy and muscle disease[130]. However, the chromosome 13 territory was found completely abutted to the nuclear periphery[129]. The authors hypothesized that changes in nuclear positioning and therefore chromatin organization, can modulate the epigenetic regulation of gene expression. This may be via altering interactions with active transcription complexes and subsequent accessibility to transcription factors[131–134] (Fig. 1). Interestingly, cells lacking A-type Lamins have defective nuclear mechanics and impaired expression of mechanosensitive genes such as *iex-1* and *egr-1*[122]. Further evidence that Lamin A/C may play a mechanosensing role is from studies using $lmna^{+/-}$ mice. These mice display a significantly attenuated response to pressure overload, evidenced by reduced ventricular mass and myocyte size [135]. In addition, analysis of pressure-overload induced transcriptional changes also revealed an impaired activation of *egr-1*. The most recent data suggesting Lamin A/C plays a role as a mechanosensor was derived from analysis of Lamin A/C null mice or Lamin (N195K/N195K) mutant mice [91]. MEFs derived from both mouse lines showed impaired nuclear translocation of the mechanosensitive transcription factor MKL1. Furthermore, cardiac sections from both mouse lines had significantly reduced fractions of cardiomyocytes with nuclear MKL1. MKL1 is a co-activator of SRF, which in turn is a master regulator of genes encoding many cytoskeletal proteins [136].

Many mouse models have been generated to mimic mutations found in humans, for a comprehensive overview see[137]. Interestingly, it appears that some autosomal dominant mutations in humans, for example the H222P mutation which causes AD-EDMD, only causes a phenotype in mice when both alleles are mutated[138]. Mutations in other factors or greater dosage sensitivity may exacerbate the phenotype in humans.

One of the better characterized mouse models used to mimic EDMD in humans is the $lmna^{-/-}$ mouse[77]. These mice develop severe cardiac and skeletal myopathy, bearing a striking resemblance to human EDMD, which results in premature death between 6–8 weeks of postnatal development. $lmna^{-/-}$ MEFs and tissues exhibit aberrant nuclear morphology, partial loss of peripheral heterochromatin, and mislocalization of Emerin[77]. In another study using the same $lmna^{-/-}$ model, mutant mice develop rapidly progressive DCM by 4–6 weeks of age[139]. Isolated $lmna^{-/-}$ cardiomyocytes exhibit altered nuclear morphology and

architecture with central displacement and fragmentation of heterochromatin. These studies lend further credence to the notion that Lamins and their associated proteins play an important role in nuclear mechanics, chromatin organization, and modulation of gene expression, which if impaired causes striated muscle damage in subjects with certain Lamin A/C mutations.

A recent report demonstrated that the original *lmna*$^{-/-}$ mouse is not a null-allele and actually expresses a truncated form of Lamin A that arises as a result of an unforeseen splicing event[69]. The resulting protein is 54 kDa in size, and contains the N-terminal globular domain and rod domains, whereas a large proportion of the C-terminal globular domain is missing[69]. The C-terminus is where most of the interaction partners are thought to bind to Lamin A, hence many of the conclusions from the *lmna*$^{-/-}$ mouse are still likely to be valid.

In another Lamin mutant mouse line generated using gene-trap technology, *lmna*$^{GT-/-}$ mice have a more severe phenotype than the *lmna*$^{-/-}$ mice, and die before weaning at 2–3 weeks post partum, providing evidence that the truncated Lamin A protein in *lmna*$^{-/-}$ mutants retains some function[140]. The phenotype of *lmna*$^{GT-/-}$ mice is more consistent with what is observed in humans, as a patient that lacked Lamin A/C died at birth[141]. Clearly, some re-evaluation is required of the data collected from the *lmna*$^{-/-}$ mouse, despite the value it has added to the field in terms of understanding laminopathies.

Unlike A-type Lamins, there are a paucity of diseases linked to mutations in B-type Lamins. This may be because mutations result in early lethality, as observed for Lamin B1 knock-down mice, and Lamin B2 knock-out mice[142–144]. To date, no B-type Lamin mutations have been reported as causing either skeletal or cardiac myopathies.

Concluding remarks and future directions

The importance of the LINC complex in numerous fundamental cellular functions has been established by the discovery of cardiac and skeletal muscle disease-causing mutations in genes encoding LINC complex-associated proteins[17–21, 36, 39, 42, 45]. The LINC complex provides structural support to the nucleus and physically couples the nucleoskeleton with the cytoskeleton[7–11] and is hypothesized to serve as a mechanosensor, translating mechanical cues, which include physical forces and alterations in ECM mechanics, into biochemical signals[12, 13]. By mediating changes in cytoskeletal and nuclear organization, structure, and positioning, these mechanical signals may also influence chromatin localization, and regulate gene expression[12–16]. These mechanisms are not mutually exclusive, and alterations in one of these cellular features could influence the other. Consequently, any disruption in the LINC-associated protein complex could result in defects in cellular structure and function and so contribute to the development of cardiac and skeletal myopathies, as described throughout this review.

The use of integrated approaches that combine animal models and cell-based assays where LINC complex-associated proteins have been targeted, has been instrumental in beginning to uncover the molecular mechanism(s) by which NE proteins act as crucial regulators in diverse cellular processes. These include cytoskeletal organization, nuclear architecture,

chromatin dynamics, and gene expression. The next step is to determine molecular mechanisms by which cardiac and skeletal muscle-specific complexes coordinate mechanical and signaling pathways throughout the cell, and how malfunction of this process contributes to disease.

As described in this review, a number of NE-associated proteins, including Nesprins, SUNs, Emerin, Luma, and Lamins, have been studied in detail. To further investigate their involvement in cardiac and skeletal muscle function, future work should involve more in-depth studies characterizing each of the individual proteins, and individual isoforms, by generating global and cardiac specific knock-out mice for each of the proteins and specific isoforms. Another key future challenge is to further determine LINC complex interaction networks with other NE-associated and proximal proteins, as well as yet to be identified proteins, in cardiomyocytes.

It is also important to generate mouse models that mimic disease mutations identified in humans to elucidate molecular mechanisms underlying cardiac and skeletal myopathies in vivo. Furthermore, complementary studies are essential to investigate mechanisms by which mutations in LINC complex-associated proteins impact human cardiomyocyte function, utilizing human patient-derived iPSCs. In addition to uncovering fundamental biology, insights gained from these studies can potentially lead to novel therapeutic approaches for treating the devastating diseases caused by LINC complex-associated mutations, including cardiac and skeletal myopathies.

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Non-standard Abbreviations and Acronyms

ABD	actin-binding domain
AC	arrhythmogenic cardiomyopathy
AD	autosomal dominant
ARVC	arrhythmogenic right ventricular cardiomyopathy
BAF	barrier to auto-integration factor
CH	calponin-homology
DCM	dilated cardiomyopathy
DKO	double knock-out
ECM	extracellular matrix

EDMD	Emery-Dreifuss muscular dystrophy
INM	inner nuclear membrane
iPSC	induced pluripotent stem cell
HP1	heterochromatin protein 1
KASH	Klarsicht, ANC-1, and Syne homology
LBR	Lamin B receptor
LINC	linker of nucleoskeleton and cytoskeleton
MEF	Mouse Embryonic Fibroblast
MKL1	megakaryoblastic leukaemia 1
NE	nuclear envelope
NELS	nuclear envelope localization signal
Nesprin	nuclear envelope spectrin-repeat protein
NLS	nuclear localization signal
NPC	nuclear pore complex
NUANCE	nucleus and actin connecting element
MEF	mouse embryonic fibroblast
Myne	myocyte nuclear envelope protein
ONM	outer nuclear membrane
PNS	perinuclear space
PVC	premature ventricular contractions
RACE	rapid amplification cDNA ends
SR	spectrin-repeat
SUN	Sad1/UNC-84
Syne	synaptic nuclear envelope
TM	transmembrane
VSMC	vascular smooth muscle cell

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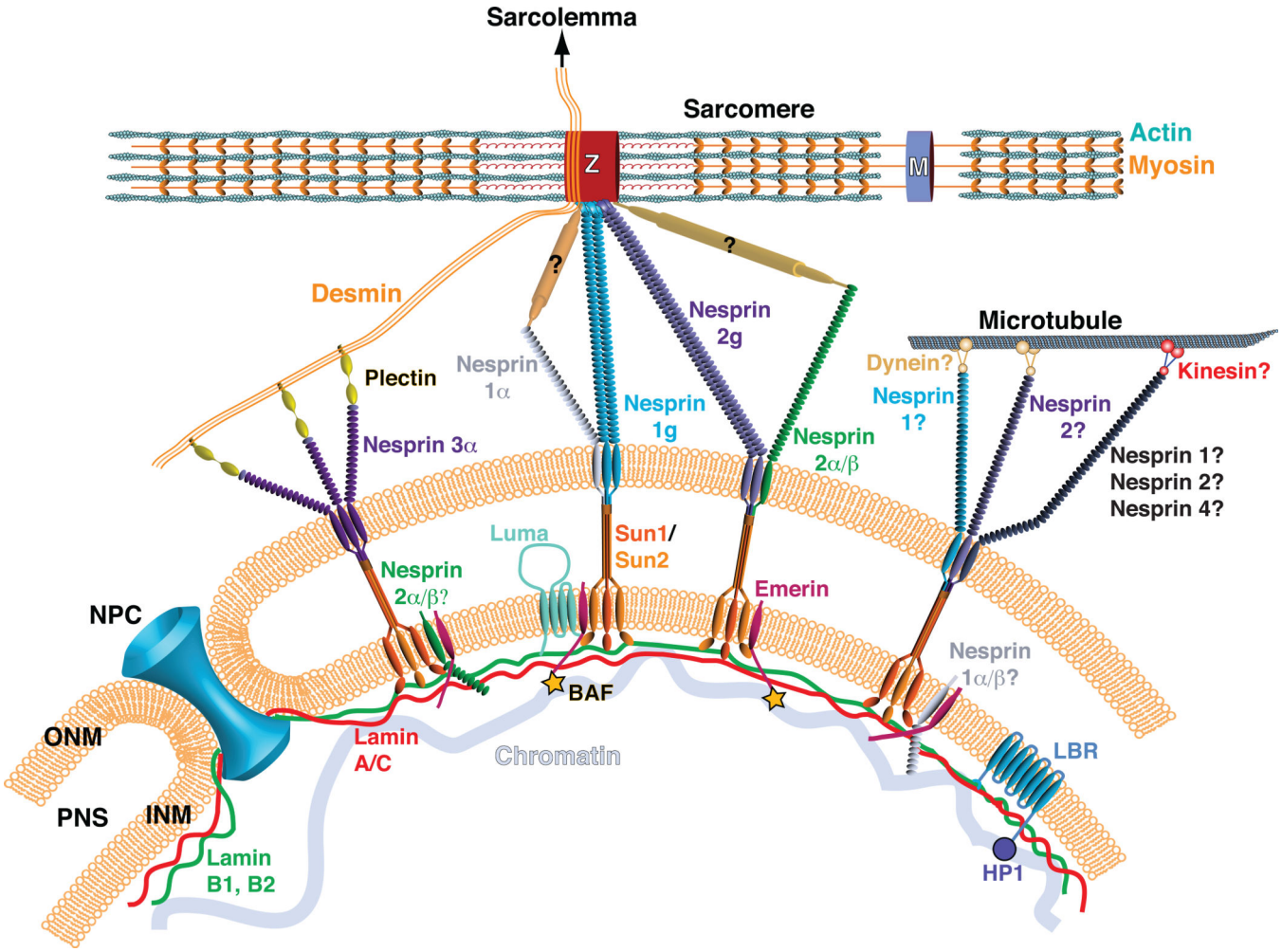

Figure 1. The LINC complex in the cardiomyocyte

The LINC complex couples the nuclear lamina to the cytoskeleton. SUN domain proteins, SUN1 and SUN2, located at the inner nuclear membrane (INM) interact with the nuclear lamins, Lamin A/C, B1 and B2, that line the nucleoplasmic face of the INM. SUN domain proteins interact with Nesprins in the perinuclear space (PNS). Nesprins protrude from the outer nuclear membrane (ONM) and interact with the cytoskeleton, often through an intermediate binding partner. Nesprin 1 giant (g) and 2g potentially link the NE directly to the Z-disc (Z), whereas Nesprin 1α and 2α may connect via an unknown intermediate protein. In addition, the shorter isoforms of Nesprin 1 and 2 may localize to the INM. Various proteins are associated with the LINC complex, such as Emerin and Luma, and are thought to play an important role in cardiac function. Chromatin directly interacts with Lamin A/C and indirectly with Emerin and Lamin B Receptor (LBR) via Barrier to Auto-integration Factor (BAF) and Heterochromatin Protein 1 (HP1), respectively. NPC, Nuclear Pore Complex; M, M-band.