



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

The increasing relevance of nuclear envelope myopathies

Citation for published version:

Meinke, P & Schirmer, EC 2016, 'The increasing relevance of nuclear envelope myopathies' Current opinion in neurology, vol. 29, no. 5, pp. 651–661. DOI: 10.1097/WCO.0000000000000359

Digital Object Identifier (DOI):

[10.1097/WCO.0000000000000359](https://doi.org/10.1097/WCO.0000000000000359)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Current opinion in neurology

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



The Increasing Relevance of Nuclear Envelope Myopathies

Peter Meinke^{a,b} and Eric C Schirmer^{b,*}

^aFriedrich-Baur Institute, Munich, Germany; ^bWellcome Trust Centre for Cell Biology,
University of Edinburgh, Edinburgh, UK

*Corresponding author:

Dr. Eric C. Schirmer

The Wellcome Trust Centre for Cell Biology

University of Edinburgh, Kings Buildings

Michael Swann Building, Room 5.22

Max Born Crescent

Edinburgh, EH9 3BF, UK

Phone: +441316507075

Fax: +441316507360

E-Mail: e.schirmer@ed.ac.uk

Abstract:**Purpose of review**

Nuclear envelope links to a wide range of disorders including several myopathies and neuropathies over the past two decades has spurred research leading to a completely changed view of this important cellular structure and its functions. However, the many functions now assigned to the nuclear envelope make it increasingly hard to determine which functions underlie these disorders.

Recent findings

New nuclear envelope functions in genome organization, regulation, and repair, signaling, and nuclear and cellular mechanics have been added to its classical barrier function. Arguments can be made for any of these functions mediating pathology in nuclear envelope disorders and data exists supporting many. Moreover, transient and/or distal nuclear envelope connections to other cellular proteins and structures may increase the complexity of these disorders.

Summary

Although the increased understanding of nuclear envelope functions has made it harder to distinguish specific causes of nuclear envelope disorders, this is because it has greatly expanded the spectrum of possible mechanisms underlying them. This change in perspective applies well beyond the known nuclear envelope disorders, potentially implicating the nuclear envelope in a much wider range of myopathies and neuropathies.

Keywords

nuclear envelope; muscular dystrophy; neuropathy; gene expression; cytoskeleton

Introduction

The nuclear envelope (NE) is a structurally complex double membrane system perforated by nuclear pore complexes that encloses the genome in eukaryotic cells (Fig. 1). The outer nuclear membrane (ONM) is continuous with the endoplasmic reticulum (ER) [1]. It contains both ER proteins and several NE transmembrane (NET) proteins, some both interacting with cytoskeletal proteins and connecting across the lumen to inner nuclear membrane (INM) proteins [2, 3]. The INM contains many NETs and is underlaid by an intermediate filament meshwork of nuclear lamins [4, 5]. Mutations in both NETs and lamins are linked to over two-dozen disorders ranging from muscular dystrophies to neuropathies, dermatopathies, lipodystrophies and premature aging syndromes [6[■], 7] (Table 1).

The discovery that emerin, the first gene linked to Emery-Dreifuss muscular dystrophy (EDMD) [8], is a NET [9] raised a central question: how can disruption of NE functions cause myopathies? Subsequent findings that lamin A mutations cause another EDMD variant [10] and emerin binds lamin A [11] suggested that functions disrupted in EDMD are supported by larger protein complexes. Searching for functions shared by emerin and lamin A quickly led to newly identified NE functions in cell cycle regulation, signaling, and genome regulation [12-15]. As lamins are intermediate filaments, cytoskeletal mechanics was also investigated, finding weakened mechanical stability of nuclei and cells for both lamin and emerin disruption [16, 17]. While these discoveries were being made several other NE proteins were linked to EDMD [18, 19[■], 20], further complicating the task of determining the NE functions most important for driving EDMD pathology.

Concomitant with the expansion of EDMD-linked genes, a wide variety of other diseases were being linked to NE proteins, collectively termed laminopathies — primary laminopathies for mutations in lamins and secondary laminopathies for mutations in associated proteins. These included other muscle diseases such as a variant of limb-girdle muscular dystrophy (LGMD1B) [21], and familial cardiomyopathy with conduction defect

[22], but also included disorders affecting different tissues. A variant of Charcot-Marie Tooth Neuropathy (CMT-2B) was linked to other lamin A mutations [23] while another brain disorder affecting myelin was linked to lamin B1 mutations [24] and cerebellar ataxia to the NET nesprin 1 [25]. Several lipodystrophies [26, 27], dermatopathy [28], osteopoikilosis and melorheostosis [29], Greenberg-Skeletal dysplasia [30], Pelger-Huet anomaly [31], and several progeroid syndromes [32, 33] were also linked to lamin and NET mutations. Mutations in lamin A are responsible for several of these disorders affecting separately muscle, fat, skin and neurons, which prompted another central question for the field: how do mutations in widely expressed proteins cause distinct tissue specific diseases?

LGMD and CMT are, like EDMD, both genetically heterogeneous diseases. However, whereas EDMD is linked to just NE protein-encoding genes, LGMD and CMT are linked to genes encoding proteins from all over the cell. Nonetheless, 40% of proteins are estimated to have multiple cellular locations [34] and roughly a third of LGMD-linked genes encode proteins found in proteomic analyses of the NE [35-37[■]]. This raises the final question: are these seemingly disparate proteins physically or functionally connected to yield the same disease pathologies? Recent publications have begun to shed some light on all three of the above questions.

Novel NE functions in the context of myopathy and neuropathy

NE-directed genome organization

The quest for emerin links to chromatin quickly revealed that emerin, like the NET LAP2 β [38], binds barrier-to-autointegration factor [39], a protein involved in compacting chromatin [40]. Other more specific chromatin-associated emerin binding partners include splicing factor YT521-B [41], transcriptional repressors Btf and germ cell-less [14, 42], and the Lmo7 transcription factor [43].

Muscle-specific gene expression was altered in EDMD patients and an emerin knockout mouse: specifically disruption of MyoD pathways important for muscle differentiation and regeneration [44, 45]. This could partly be explained by recent findings that emerin inhibits binding of the Lmo7 transcription factor to promoters for important myogenic genes Pax3 and MyoD [46], presumably by sequestering Lmo7 at the NE.

Finally, genome organization is disrupted in EDMD patient cells, with a visible redistribution of peripheral heterochromatin away from the NE [47, 48]. These defects were observed in both lamin and NET-linked EDMD and also in lamin A-linked cardiomyopathy [49]. The past few years have seen great strides in understanding NE-directed spatial genome organization. General NE-heterochromatin interactions are driven by the NET LBR together with lamin A [50, 51]. However, other NETs LAP2 β and emerin also contribute by recruiting the histone deacetylase HDAC3 to promote heterochromatin formation at the NE [52, 53]. Thus both lamin A and emerin contribute to NE-heterochromatin interactions.

Specific gene targeting to the NE is also regulated by NETs. A complex with LAP2 β , HDAC3, lamin B1 and the transcriptional repressor cKrox maintains the *IgH* and *Cyp3a* loci at the NE in fibroblasts [54]. A likely similar complex containing emerin and HDAC3 was subsequently found to affect the expression and nuclear positions of the *MyoD*, *Myf5* and *Pax7* genes important for myogenesis [55]. However, other proteins likely contribute to both complexes as the specific targeting and release from the periphery in certain cell types cannot be explained by the players thus far identified. This function may be assumed by several tissue-specific NETs that reposition genes and chromosomes to the NE in fibroblasts and are required for their normal positioning in tissues [35, 56, 57[■]]. Specifically in myogenesis, three muscle-specific NETs, NET39, Tmem38a and WFS1, direct important gene repositionings that enhance muscle-gene regulation [57[■]]. Genes under this regulation tend to require tight temporal regulation because their products are needed early in myogenesis, but are inhibitory at later stages. Several such as *EfnA5*, *Cxcl1* and *Ptn* are also reactivated upon

muscle damage [58, 59]. Each of the three muscle NETs largely affects distinct gene subsets, but together they affect 37% of all genes normally changing in myogenesis. Importantly, individual NET knockdowns did not block myogenesis while their combined knockdown almost completely blocked myotube formation [57^{***}]. Thus, the potential involvement of these muscle NETs in protein complexes linked to EDMD is consistent with the initial normal muscle development, then appearance of muscle wasting and contractures as children become more physically active. Such tissue-specific gene regulation defects could explain all NE disorders as similar genome organization disruption has been recently linked to limb development diseases [60^{***}].

NE Mechanical connections and tensegrity

As lamins are intermediate filaments, another proposed mechanism towards EDMD pathology is nuclear mechanical defects. Accordingly, lamin A knockout fibroblasts have reduced resistance to mechanical stress and exhibit defects in cell migration [16, 61]. Emerin knockout also alters NE elasticity [17] and emerin has an additional role in capping actin filaments [62]. Nonetheless, the strongest argument for the mechanical hypothesis was the additional linking of nesprin and SUN mutations to EDMD [18, 19^{***}]. Nesprins and SUN proteins are NETs that connect across the lumen of the NE with a triple helical interface [63, 64]. Nesprins in the ONM further connect to cytoplasmic filament systems [65-69^{***}] while SUNs in the INM connect to the lamin polymer [70, 71]. The protein complex containing SUNs and nesprins is named LINC for linker of nucleo- and cytoskeleton [3].

Nesprin-nesprin interactions are proposed to form a scaffold on the ONM, providing further mechanical stability [72]. SUN1 and 2 are partially redundant [73] and nesprin 1 and 2 may be also [74, 75^{***}], but each can likely fulfill separate tissue specific functions. SUN2 forms distinct LINC complexes during meiosis [76[■]] and distinctive LINC complexes containing either nesprin 1 or the SUN1 isoform SUN1 η appear during sperm development

[77]. Tellingly, the distinct LINC complexes localize to opposite poles of the spermatid [77]. Other LINC complexes characterized by the additional partner NET5 (TMEM201/Samp1) associate with TAN-lines that serve as tracks for nuclear migration and positioning within the cell [78]. Tissue-specific isoforms of NET5 and nesprins have been identified [56, 79, 80[■]].

The partial redundancy and many SUN and nesprin isoforms make it hard to distinguish the roles of each protein in disease, but mouse models show tissue specific effects. LINC complexes are particularly critical for neurogenesis [81] with nesprin 1/2 double knockout mice failing to recruit synaptic nuclei to the neuromuscular junction [82] while SUN1/2 double knockout mice have abnormal synaptic nuclei [73]. Nesprin-1 disruption alone in mice yields an EDMD-like phenotype [83]. This complexity may also explain why different EDMD mutations yield distinct tissue culture phenotypes [84] and the extreme clinical variability for EDMD [19[■], 85]. Accordingly mutations in nesprin 1 have been associated with cerebellar ataxia [25], EDMD [18] and another similar muscular dystrophy [86[■]] and the same will likely apply for other NETs.

Nuclear/cellular mechanics could also affect gene expression through mechanosignal transduction. An EDMD-causing *LMNA* mutation disrupted nuclear mechanical responses specifically in muscle nuclei [87[■]]. Cells from lamin-A/C knockout mice have impaired nuclear translocation and downstream signaling of the mechanosensitive transcription factor MKL1 [88]. Moreover, the Yes-associated Protein (YAP), a transcriptional coactivator, failed to relocate to the nucleus upon nesprin knockdown [89] and *LMNA* mutant myoblasts were unable to reactivate YAP after cyclic stretch [90[■]]. Thus, lamins and NETs are involved in mechanical signaling pathways and disruption of either could yield similarities in phenotypes.

NE Signaling defects

Emerin functions intersect with the Wnt/ β -catenin pathway [12], raising the possibility that non-mechanical signaling defects could also underlie NE disease pathology. Further

evidence comes from a recent study where depletion of emerin in mouse ES cell-derived cardiomyocytes caused hyper-activation of Wnt/ β -catenin signaling, negatively affecting cardiac differentiation [91[■]]. Another NET involved in Wnt signaling is nesprin 2 by interaction with α -catenin [92]. An ortholog of nesprin 1 and 2 in *C. elegans* regulates axon termination and synapse formation, likely through Wnt/ β -catenin signaling [93[■]]. Several other NETs intersect with signaling pathways including NET59/Ncln (antagonizing Nodal signaling and TGF β pathways, [94]), MAN1 (Smad/BMP/TGF β -signaling [95, 96]), and NET25 (Lem2) (negatively regulating the ERK1/2 pathway [97]). NET25 is required for efficient myoblast differentiation and complements emerin's role in myogenesis [97]. NET39, which is principally expressed in heart and skeletal muscle [98], acts on the mTOR pathway in myogenesis [99].

Lamin A is involved in several signaling pathways including MAP kinase [100] and Wnt/ β -catenin during early mesenchymal stem cell differentiation [101]. Elevated ERK1/2 signaling in *LMNA* linked cardiomyopathy is modulated by TGF- β /Smad signaling [37[■]] and myopathic lamin A mutations activate the nrf2/keap-1 pathway [102]. For the latter, cytoplasmic lamin aggregates induced by reductive stress correlate with elevated levels of the autophagy adaptor p62/SQSTM1 that binds the cytoplasmic nrf2 interactor keap-1, thus allowing nrf2 nuclear translocation and target gene activation [102[■]]. Finally, Akt/mTOR signaling is hyper-activated in hearts of mice carrying an EDMD-causing *LMNA* mutation [36].

Thus, several signaling pathways are regulated by NE proteins. Due to the availability of existing drugs targeting these pathways, they are a promising avenue for treatment of the heart effects in NE-linked myopathies [103]. However, most of these pathways are active in a wide range of cell types and so other factors may contribute to tissue specificity in pathologies.

Tissue specific functioning of the NE in myopathies and neuropathies

NE Tissue specificity

One way to explain how mutations in ubiquitously expressed proteins yield tissue-specific defects is if larger complexes including tissue-specific proteins are required for the functions affected. Several studies over the past 5 years have demonstrated that each tissue sampled has a distinct subset of NETs [35, 104, 105]. Tissue transcriptomic comparisons with the tissues thus far sampled by NE proteomics indicates that other tissues such as brain and skin likely have completely distinct NE proteomes [6[■]]. Therefore it may be necessary to determine NE proteomes for each tissue where pathology is observed before all NE diseases can be fully explained.

Thus far, muscle-specific NETs have been identified with functions in cytoskeletal organization [104] that fit with the mechanical instability hypothesis while those affecting genome organization [57[■]] fit with the gene regulation hypothesis. Mechanical stress is less likely to underlie neuropathies and lipodystrophies. However, a fat-specific NET that affected genome organization [56] was required for adipogenesis [106[■]], suggesting that tissue-specific NETs in genome regulation could apply for all NE-linked disorders.

Calcium signaling at the NE

The muscle NE proteome was enriched in Ca²⁺ signaling and ion transport proteins [104]. Though many of these proteins are not tissue-specific, they are only at the NE in muscle, suggesting tissue-specific targeting could also explain NE-linked tissue-specific pathologies. Some proteins mutated in other muscular dystrophies are involved in calcium transport, including dystrophin and calpain 3 [107, 108[■], 109[■]-111]. Calpain 3 knockout mice have attenuated Ca²⁺ release and Ca²⁺/calmodulin signaling, resulting in a failure to transmit loading-induced Ca²⁺ mediated signals, necessary to up-regulate expression of muscle adaptation genes [112[■]].

Functional connections of multi-compartmental proteins

Several proteins historically linked to other cellular compartments are now directly shown to be also associated with the NE and many of these have links to related diseases. For example, plectin is a cytoplasmic filament-crosslinking protein linked to LGMD [113]. Plectin was identified in NE proteomes and associates with nesprin 3 in the ONM [67, 105]. Loss of plectin isoform P1 yields altered nuclear morphology, mechanotransduction, chromatin modifications and gene expression [114[■]]. POPDC proteins, originally thought to be at the plasma membrane, were also found in muscle NE proteomes and have been confirmed at the NE [104]. POPDC1 was recently linked to LGMD [115[■]]. POPDC1 has also been identified in the NE. The best example of how characterized plasma membrane proteins can also function in the nucleus is caveolin. While LGMD-linked caveolin 3 is only found in muscle, caveolin 1 and 2 are ubiquitously expressed. Caveolin 2 translocates to the nucleus and interacts with lamin A thereby disengaging repressed promoters from lamin A/C through epigenetic regulation of histone H3 modifications [116[■]]. In all roughly 1/3 of LGMD-linked proteins were found in NE proteomics datasets (Table 2); so many more variants than lamin-linked LGMD may yield pathology through NE functions.

The same concept likely accounts for proteins linked to Bethlem myopathy, a disease similar to EDMD and potentially many other diseases. Mutations in the valosin-containing protein (VCP) gene cause inclusion body myopathy and VCP was recently found to be involved in nuclear envelope reconstruction [117]. The DNA/RNA binding protein matrin-3 linked to inherited myopathy [118] fails to interact with lamin A Δ 303, a myopathic *LMNA* mutation [119[■]]. A member of the dystrophin-associated protein complex - α -dystrobrevin - that is central to cytoskeletal organization, has also been recently found in the nucleus [120]. There it interacts with lamin B1 and knockdown resulted in morphological defects of the NE [121[■]]. The reverse direction also holds with NE proteins extending their reach into the

cytoplasm: NE-associated endosomes deliver surface proteins to the nucleus depending on SUN1 and SUN2 [122^{***}]. All the above examples show how connections between NE proteins and proteins from other cellular compartments or the compartments themselves can provide functional links that may explain NE-linked myopathies and neuropathies.

Conclusions:

While hopes of identifying a single causative mechanism for NE-linked myopathies and neuropathies have dwindled due to the explosive increase in NE functions, the expansion of data supporting various distinct mechanisms may also reflect the existence of multiple mechanisms to pathology (Fig. 2). The genome regulation, signaling and mechanical stability hypotheses all continue to gain support for NE-linked myopathies and neuropathies. However, all of these mechanisms still fail to fully explain the tissue-specificity of pathologies. While many candidate tissue-specific partners exist for muscle, it will likely be necessary to determine the brain NE proteome to answer such questions about the mechanism underlying NE-linked neuropathies.

Key points:

- Evidence for cell mechanics, gene regulation and signaling all continue to accumulate as potential mechanisms to pathology for nuclear envelope-linked myopathies and neuropathies, making determination of central causes difficult.
- Tissue-specific partners of proteins mutated in nuclear envelope-linked myopathies may mediate their muscle-specific pathologies as they impact on the mechanisms thought to underlie these diseases.
- Nuclear envelope functions discovered for proteins linked to related myopathies suggest both that these proteins may play roles in the nuclear envelope disease and that other myopathies and neuropathies might be linked to the nuclear envelope.

Acknowledgements:

We thank Dr Jose de las Heras and Dr Rafal Czapiewski for critical reading of the manuscript.

Financial support and sponsorship:

This work was supported by Wellcome Trust Senior Research Fellowship 095209 to E.C.S. and the Wellcome Trust Centre for Cell Biology core grant 092076.

Conflicts of interest:

There are no conflicts of interest.

References:

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ ■ of outstanding interest

- [1] Callan HG, Randall JT, Tomlin SG. An electron microscope study of the nuclear membrane. *Nature* 1949;163:280.
- [2] Meinke P, Schirmer EC. LINC'ing form and function at the nuclear envelope. *FEBS Lett* 2015;589:2514-21.
- [3] Crisp M, Liu Q, Roux K, et al. Coupling of the nucleus and cytoplasm: role of the LINC complex. *J Cell Biol* 2006;172:41-53.
- [4] de Las Heras JI, Meinke P, Batrakou DG, et al. Tissue specificity in the nuclear envelope supports its functional complexity. *Nucleus* 2013;4:460-77.
- [5] Wong X, Luperchio TR, Reddy KL. NET gains and losses: the role of changing nuclear envelope proteomes in genome regulation. *Curr Opin Cell Biol* 2014;28:105-20.
- [6] Worman HJ, Schirmer EC. Nuclear membrane diversity: underlying tissue-specific pathologies in disease? *Curr Opin Cell Biol* 2015;34:101-12.
- Review with bioinformatic analysis showing the likelihood of many as yet unidentified NE proteins in brain and nerves.
- [7] Bonne G, Quijano-Roy S. Emery-Dreifuss muscular dystrophy, laminopathies, and other nuclear envelopopathies. *Handb Clin Neurol* 2013;113:1367-76.
- [8] Bione S, Maestrini E, Rivella S, et al. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. *Nat Genet* 1994;8:323-7.
- [9] Manilal S, Nguyen TM, Sewry CA, Morris GE. The Emery-Dreifuss muscular dystrophy protein, emerin, is a nuclear membrane protein. *Hum Mol Genet* 1996;5:801-8.
- [10] Bonne G, Di Barletta MR, Varnous S, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet* 1999;21:285-288.
- [11] Clements L, Manilal S, Love DR, Morris GE. Direct interaction between emerin and lamin A. *Biochem Biophys Res Commun* 2000;267:709-14.
- [12] Markiewicz E, Tilgner K, Barker N, et al. The inner nuclear membrane protein emerin regulates beta-catenin activity by restricting its accumulation in the nucleus. *Embo J* 2006;25:3275-85.
- [13] Johnson BR, Nitta RT, Frock RL, et al. A-type lamins regulate retinoblastoma protein function by promoting subnuclear localization and preventing proteasomal degradation. *Proc Natl Acad Sci U S A* 2004;101:9677-82.
- [14] Holaska JM, Lee KK, Kowalski AK, Wilson KL. Transcriptional repressor germ cell-less (GCL) and barrier to autointegration factor (BAF) compete for binding to emerin in vitro. *J Biol Chem* 2003;278:6969-75.

- [15] Fairley EA, Riddell A, Ellis JA, Kendrick-Jones J. The cell cycle dependent mislocalisation of emerin may contribute to the Emery-Dreifuss muscular dystrophy phenotype. *J Cell Sci* 2002;115:341-54.
- [16] Lammerding J, Schulze PC, Takahashi T, et al. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J Clin Invest* 2004;113:370-8.
- [17] Rowat AC, Lammerding J, Ipsen JH. Mechanical properties of the cell nucleus and the effect of emerin deficiency. *Biophys J* 2006;91:4649-64.
- [18] Zhang Q, Bethmann C, Worth NF, et al. Nesprin-1 and -2 are involved in the pathogenesis of Emery Dreifuss muscular dystrophy and are critical for nuclear envelope integrity. *Hum Mol Genet* 2007;16:2816-33.
- [19] Meinke P, Mattioli E, Haque F, et al. Muscular dystrophy-associated SUN1 and SUN2 variants disrupt nuclear-cytoskeletal connections and myonuclear organization. *PLoS Genet* 2014;10:e1004605.
- ■ First association of SUN1 and SUN2 to inherited disease, showing effects on nuclear-cytoskeletal connections. This greatly strengthened support for the mechanical instability hypothesis.
- [20] Liang WC, Mitsuhashi H, Keduka E, et al. TMEM43 mutations in Emery-Dreifuss muscular dystrophy-related myopathy. *Ann Neurol* 2011;69:1005-13.
- [21] Muchir A, Bonne G, van der Kooij AJ, et al. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). *Hum Mol Genet* 2000;9:1453-9.
- [22] Fatkin D, MacRae C, Sasaki T, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;341:1715-24.
- [23] De Sandre-Giovannoli A, Chaouch M, Kozlov S, et al. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth disorder type 2) and mouse. *Am J Hum Genet* 2002;70:726-36.
- [24] Padiath QS, Saigoh K, Schiffmann R, et al. Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* 2006;38:1114-23.
- [25] Gros-Louis F, Dupre N, Dion P, et al. Mutations in SYNE1 lead to a newly discovered form of autosomal recessive cerebellar ataxia. *Nat Genet* 2007;39:80-85.
- [26] Cao H, Hegele RA. Nuclear lamin A/C R482Q mutation in canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* 2000;9:109-12.
- [27] Shackleton S, Lloyd DJ, Jackson SN, et al. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet* 2000;24:153-6.
- [28] Navarro CL, De Sandre-Giovannoli A, Bernard R B, I., et al. Lamin A and ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. *Hum Mol Genet* 2004;13:493-503.
- [29] Hellemans J, Preobrazhenska O, Willaert A, et al. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. *Nat Genet* 2004;36:1213-1218.
- [30] Waterham HR, Koster J, Mooyer P, et al. Autosomal recessive HEM/greenberg skeletal dysplasia is caused by 3 beta-hydroxysterol Delta(14)-reductase deficiency due to mutations in the lamin B receptor gene. *Am J Hum Genet* 2003;72:1013-1017.
- [31] Hoffmann K, Dreger CK, Olins AL, et al. Mutations in the gene encoding the lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger-Huet anomaly). *Nat Genet* 2002;31:410-414.
- [32] De Sandre-Giovannoli A, Bernard R, Cau P, et al. Lamin A truncation in Hutchinson-Gilford progeria. *Science* 2003;300:2055-2055.

- [33] Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* 2003;423:293-298.
- [34] Foster LJ, de Hoog CL, Zhang Y, Xie X, Mootha VK, Mann M. A mammalian organelle map by protein correlation profiling. *Cell* 2006;125:187-99.
- [35] Korfali N, Wilkie GS, Swanson SK, et al. The leukocyte nuclear envelope proteome varies with cell activation and contains novel transmembrane proteins that affect genome architecture. *Mol Cell Proteomics* 2010;9:2571-85.
- [36] Choi JC, Worman HJ. Reactivation of autophagy ameliorates LMNA cardiomyopathy. *Autophagy* 2013;9:110-1.
- [37] Chatzifrangkeskou M, Le Dour C, Wu W, et al. ERK1/2 directly acts on CTGF/CCN2 expression to mediate myocardial fibrosis in cardiomyopathy caused by mutations in the lamin A/C gene. *Hum Mol Genet* 2016.
- TGF- β /Smad signaling modulates ERK1/2 activity in *LMNA* linked cardiomyopathy, providing both a potential therapeutic target and a functional link between multiple proteins causative of EDMD.
- [38] Furukawa K. LAP2 binding protein 1 (L2BP1/BAF) is a candidate mediator of LAP2-chromatin interaction. *J Cell Sci* 1999;112 (Pt 15):2485-92.
- [39] Lee KK, Haraguchi T, Lee RS, Koujin T, Hiraoka Y, Wilson KL. Distinct functional domains in emerin bind lamin A and DNA-bridging protein BAF. *J Cell Sci* 2001;114:4567-73.
- [40] Zheng R, Ghirlando R, Lee MS, Mizuuchi K, Krause M, Craigie R. Barrier-to-autointegration factor (BAF) bridges DNA in a discrete, higher-order nucleoprotein complex. *Proc Natl Acad Sci U S A* 2000;97:8997-9002.
- [41] Wilkinson FL, Holaska JM, Zhang Z, et al. Emerin interacts in vitro with the splicing-associated factor, YT521-B. *Eur J Biochem / FEBS* 2003;270:2459-66.
- [42] Haraguchi T, Holaska JM, Yamane M, et al. Emerin binding to Btf, a death-promoting transcriptional repressor, is disrupted by a missense mutation that causes Emery-Dreifuss muscular dystrophy. *Eur J Biochem / FEBS* 2004;271:1035-45.
- [43] Holaska JM, Rais-Bahrami S, Wilson KL. Lmo7 is an emerin-binding protein that regulates the transcription of emerin and many other muscle-relevant genes. *Hum Mol Genet* 2006;15:3459-72.
- [44] Bakay M, Wang Z, Melcon G, et al. Nuclear envelope dystrophies show a transcriptional fingerprint suggesting disruption of Rb-MyoD pathways in muscle regeneration. *Brain* 2006;129:996-1013.
- [45] Melcon G, Kozlov S, Cutler DA, et al. Loss of emerin at the nuclear envelope disrupts the Rb1/E2F and MyoD pathways during muscle regeneration. *Hum Mol Genet* 2006;15:637-51.
- [46] Dedeic Z, Cetera M, Cohen TV, Holaska JM. Emerin inhibits Lmo7 binding to the Pax3 and MyoD promoters and expression of myoblast proliferation genes. *J Cell Sci* 2011;124:1691-702.
- [47] Fidzianska A, Toniolo D, Hausmanowa-Petrusewicz I. Ultrastructural abnormality of sarcolemmal nuclei in Emery-Dreifuss muscular dystrophy (EDMD). *J Neurol Sci* 1998;159:88-93.
- [48] Sewry CA, Brown SC, Mercuri E, et al. Skeletal muscle pathology in autosomal dominant Emery-Dreifuss muscular dystrophy with lamin A/C mutations. *Neuropathol Appl Neurobiol* 2001;27:281-90.
- [49] Verga L, Concardi M, Pilotto A, et al. Loss of lamin A/C expression revealed by immuno-electron microscopy in dilated cardiomyopathy with atrioventricular block caused by LMNA gene defects. *Virchows Arch* 2003;443:664-71.

- [50] Ye Q, Worman HJ. Interaction between an integral protein of the nuclear envelope inner membrane and human chromodomain proteins homologous to *Drosophila* HP1. *J Biol Chem* 1996;271:14653-6.
- [51] Solovei I, Wang AS, Thanisch K, et al. LBR and lamin A/C sequentially tether peripheral heterochromatin and inversely regulate differentiation. *Cell* 2013;152:584-98.
- [52] Demmerle J, Koch AJ, Holaska JM. The nuclear envelope protein emerin binds directly to histone deacetylase 3 (HDAC3) and activates HDAC3 activity. *J Biol Chem* 2012;287:22080-8.
- [53] Nili E, Cojocaru GS, Kalma Y, et al. Nuclear membrane protein LAP2beta mediates transcriptional repression alone and together with its binding partner GCL (germ-cell-less). *J Cell Sci* 2001;114:3297-307.
- [54] Zullo JM, Demarco IA, Pique-Regi R, et al. DNA sequence-dependent compartmentalization and silencing of chromatin at the nuclear lamina. *Cell* 2012;149:1474-87.
- [55] Demmerle J, Koch AJ, Holaska JM. Emerin and histone deacetylase 3 (HDAC3) cooperatively regulate expression and nuclear positions of MyoD, Myf5, and Pax7 genes during myogenesis. *Chromosome Res* 2013;21:765-79.
- [56] Zuleger N, Boyle S, Kelly DA, et al. Specific nuclear envelope transmembrane proteins can promote the location of chromosomes to and from the nuclear periphery. *Genome Biol* 2013;14:2013-14.
- [57] Robson MI, de las Heras JI, Czapiewski R, et al. Tissue-specific repositioning by muscle nuclear membrane proteins enhances repression of critical developmental genes during myogenesis. *Mol Cell* 2016;62:1-14.
- ■ Identification of muscle specific NETs that direct spatial positioning changes during myogenesis for critical myogenic genes. The ability to manipulate gene position by targeting these NETs independently of differentiation enabled quantification the NET contribution to gene regulation at ~50%. This makes these muscle NETs strong candidates for mediating muscle-specific pathologies, thus arguing for the gene regulation hypothesis in EDMD.
- [58] Caruelle D, Mazouzi Z, Husmann I, et al. Upregulation of HARP during in vitro myogenesis and rat soleus muscle regeneration. *J Muscle Res Cell Motil* 2004;25:45-53.
- [59] Stark DA, Karvas RM, Siegel AL, Cornelison DD. Eph/ephrin interactions modulate muscle satellite cell motility and patterning. *Development* 2011;138:5279-89.
- [60] Lupianez DG, Kraft K, Heinrich V, et al. Disruptions of topological chromatin domains cause pathogenic rewiring of gene-enhancer interactions. *Cell* 2015;161:1012-25.
- ■ The finding that mutations in an enhancer can alter spatial genome organization and cause developmental disease is a strong argument for the lamin/NET effects on genome organization underlying myopathy and neuropathy pathologies.
- [61] Lee JS, Hale CM, Panorchan P, et al. Nuclear lamin A/C deficiency induces defects in cell mechanics, polarization, and migration. *Biophys J* 2007;93:2542-52.
- [62] Holaska JM, Kowalski AK, Wilson KL. Emerin caps the pointed end of actin filaments: evidence for an actin cortical network at the nuclear inner membrane. *PLoS Biol* 2004;2:E231.
- [63] Zhou Z, Du X, Cai Z, et al. Structure of Sad1-UNC84 homology (SUN) domain defines features of molecular bridge in nuclear envelope. *J Biol Chem* 2012;287:5317-26.

- [64] Sosa BA, Rothballer A, Kutay U, Schwartz TU. LINC Complexes Form by Binding of Three KASH Peptides to Domain Interfaces of Trimeric SUN Proteins. *Cell* 2012;149:1035–1047.
- [65] Zhen YY, Libotte T, Munck M, Noegel AA, Korenbaum E. NUANCE, a giant protein connecting the nucleus and actin cytoskeleton. *J Cell Sci* 2002;115:3207-22.
- [66] Zhang Q, Ragnauth C, Greener MJ, Shanahan CM, Roberts RG. The nesprins are giant actin-binding proteins, orthologous to *Drosophila melanogaster* muscle protein MSP-300. *Genomics* 2002;80:473-81.
- [67] Wilhelmson K, Litjens SH, Kuikman I, et al. Nesprin-3, a novel outer nuclear membrane protein, associates with the cytoskeletal linker protein plectin. *J Cell Biol* 2005;171:799-810.
- [68] Roux KJ, Crisp ML, Liu Q, et al. Nesprin 4 is an outer nuclear membrane protein that can induce kinesin-mediated cell polarization. *Proc Natl Acad Sci U S A* 2009;106:2194-2199.
- [69] Wilson MH, Holzbaur EL. Nesprins anchor kinesin-1 motors to the nucleus to drive nuclear distribution in muscle cells. *Development* 2015;142:218-28.
- This expands on earlier studies showing nesprin involvement in nuclear positioning by using live cell imaging to show that this positioning is dynamic and depends also on motor proteins.
- [70] Haque F, Lloyd DJ, Smallwood DT, et al. SUN1 interacts with nuclear lamin A and cytoplasmic nesprins to provide a physical connection between the nuclear lamina and the cytoskeleton. *Mol Cell Biol* 2006;26:3738-3751.
- [71] Ostlund C, Folker ES, Choi JC, Gomes ER, Gundersen GG, Worman HJ. Dynamics and molecular interactions of linker of nucleoskeleton and cytoskeleton (LINC) complex proteins. *J Cell Sci* 2009;122:4099-108.
- [72] Lu W, Schneider M, Neumann S, et al. Nesprin interchain associations control nuclear size. *Cell Mol Life Sci* 2012;69:3493-509.
- [73] Lei K, Zhang X, Ding X, et al. SUN1 and SUN2 play critical but partially redundant roles in anchoring nuclei in skeletal muscle cells in mice. *Proc Natl Acad Sci U S A* 2009;106:10207-12.
- [74] Wheeler MA, Davies JD, Zhang Q, et al. Distinct functional domains in nesprin-1alpha and nesprin-2beta bind directly to emerin and both interactions are disrupted in X-linked Emery-Dreifuss muscular dystrophy. *Exp Cell Res* 2007;313:2845-57.
- [75] Banerjee I, Zhang J, Moore-Morris T, et al. Targeted ablation of nesprin 1 and nesprin 2 from murine myocardium results in cardiomyopathy, altered nuclear morphology and inhibition of the biomechanical gene response. *PLoS Genet* 2014;10:e1004114.
- Identification of a mechanosensing gene regulation function for nesprins 1 and 2 in cardiomyocytes. This importantly counters the mechanical stability hypothesis, showing that mechanical/skeletal proteins can also function in gene regulation.
- [76] Link J, Leubner M, Schmitt J, et al. Analysis of meiosis in SUN1 deficient mice reveals a distinct role of SUN2 in mammalian meiotic LINC complex formation and function. *PLoS Genet* 2014;10:e1004099.
- This supports cell-type specific complexes and functions for a widely expressed NET.
- [77] Gob E, Schmitt J, Benavente R, Alsheimer M. Mammalian sperm head formation involves different polarization of two novel LINC complexes. *PLoS One* 2010;5:e12072.
- [78] Borrego-Pinto J, Jegou T, Osorio DS, et al. Samp1 is a component of TAN lines and is required for nuclear movement. *J Cell Sci* 2012;125:1099-105.
- [79] Rajgor D, Mellad JA, Autore F, Zhang Q, Shanahan CM. Multiple novel nesprin-1 and nesprin-2 variants act as versatile tissue-specific intracellular scaffolds. *PLoS One* 2012;7:e40098.

- [80] Duong NT, Morris GE, Lam le T, et al. Nesprins: tissue-specific expression of epsilon and other short isoforms. *PLoS One* 2014;9:e94380.
- Excellent overview for the nesprin isoforms identified thus far and their often tissue-specific expression.
- [81] Zhang X, Lei K, Yuan X, et al. SUN1/2 and Syne/Nesprin-1/2 complexes connect centrosome to the nucleus during neurogenesis and neuronal migration in mice. *Neuron* 2009;64:173-87.
- [82] Zhang X, Xu R, Zhu B, et al. Syne-1 and Syne-2 play crucial roles in myonuclear anchorage and motor neuron innervation. *Development* 2007;134:901-8.
- [83] Puckelwartz MJ, Kessler E, Zhang Y, et al. Disruption of nesprin-1 produces an Emery Dreifuss muscular dystrophy-like phenotype in mice. *Hum Mol Genet* 2009;18:607-20.
- [84] Taranum S, Vaylann E, Meinke P, et al. LINC complex alterations in DMD and EDMD/CMT fibroblasts. *Eur J Cell Biol* 2012;91:614-28.
- [85] Li P, Meinke P, Huong le TT, Wehnert M, Noegel AA. Contribution of SUN1 mutations to the pathomechanism in muscular dystrophies. *Human mutation* 2014;35:452-61.
- [86] Fanin M, Savarese M, Nascimbeni AC, et al. Dominant muscular dystrophy with a novel SYNE1 gene mutation. *Muscle Nerve* 2015;51:145-7.
- An addition to the spectrum of nesprin 1-linked phenotypes.
- [87] Zuela N, Zwerger M, Levin T, Medalia O, Gruenbaum Y. Impaired mechanical response of an EDMD mutation leads to motility phenotypes that are repaired by loss of prenylation. *J Cell Sci* 2016;129:1781-91.
- Defective mechanical responses with EDMD mutations were observed specifically in muscle nuclei in worms that also exhibited motility defects. Interestingly, though lamin prenylation has been principally linked to progeroid syndromes, inhibiting lamin prenylation rescued the muscle phenotype.
- [88] Ho CY, Jaalouk DE, Vartiainen MK, Lammerding J. Lamin A/C and emerin regulate MKL1-SRF activity by modulating actin dynamics. *Nature* 2013;497:507-11.
- [89] Driscoll TP, Cosgrove BD, Heo SJ, Shurden ZE, Mauck RL. Cytoskeletal to Nuclear Strain Transfer Regulates YAP Signaling in Mesenchymal Stem Cells. *Biophys J* 2015;108:2783-93.
- [90] Bertrand AT, Ziaei S, Ehret C, et al. Cellular microenvironments reveal defective mechanosensing responses and elevated YAP signaling in LMNA-mutated muscle precursors. *J Cell Sci* 2014;127:2873-84.
- Identification of an additional mechanosensing pathway affected in LMNA-mutated myoblasts.
- [91] Stubenvoll A, Rice M, Wietelmann A, Wheeler M, Braun T. Attenuation of Wnt/beta-catenin activity reverses enhanced generation of cardiomyocytes and cardiac defects caused by the loss of emerin. *Hum Mol Genet* 2015;24:802-13.
- A potential function for emerin constraining β -catenin signaling in the heart is shown. Thus could provide a mechanism for controlling cardiomyocyte numbers and thus explain NE-linked cardiomyopathy by failure to replace damaged tissue.
- [92] Neumann S, Schneider M, Daugherty RL, et al. Nesprin-2 interacts with α -catenin and regulates Wnt signaling at the nuclear envelope. *J Biol Chem* 2010;285:34932-8.
- [93] Tulgren ED, Turgeon SM, Opperman KJ, Grill B. The Nesprin family member ANC-1 regulates synapse formation and axon termination by functioning in a pathway with RPM-1 and beta-Catenin. *PLoS Genet* 2014;10:e1004481.
- Nesprins are linked to signaling pathways important for neuronal development, thus supporting signaling defects in NE-linked neuropathy.

- [94] Haffner C, Dettmer U, Weiler T, Haass C. The Nicastrin-like protein Nicalin regulates assembly and stability of the Nicalin-nodal modulator (NOMO) membrane protein complex. *J Biol Chem* 2007;282:10632-8.
- [95] Osada S, Ohmori SY, Taira M. XMAN1, an inner nuclear membrane protein, antagonizes BMP signaling by interacting with Smad1 in *Xenopus* embryos. *Development* 2003;130:1783-94.
- [96] Raju GP, Dimova N, Klein PS, Huang HC. SANE, a novel LEM domain protein, regulates bone morphogenetic protein signaling through interaction with Smad1. *J Biol Chem* 2003;278:428-37.
- [97] Huber MD, Guan T, Gerace L. Overlapping functions of nuclear envelope proteins NET25 (Lem2) and emerin in regulation of extracellular signal-regulated kinase signaling in myoblast differentiation. *Mol Cell Biol* 2009;29:5718-28.
- [98] Wu C, Orozco C, Boyer J, et al. BioGPS: an extensible and customizable portal for querying and organizing gene annotation resources. *Genome Biol* 2009;10:R130.
- [99] Liu GH, Guan T, Datta K, Coppinger J, Yates J, 3rd, Gerace L. Regulation of myoblast differentiation by the nuclear envelope protein NET39. *Mol Cell Biol* 2009;29:5800-12.
- [100] Muchir A, Worman HJ. Targeting Mitogen-Activated Protein Kinase Signaling in Mouse Models of Cardiomyopathy Caused by Lamin A/C Gene Mutations. *Methods Enzymol* 2016;568:557-80.
- [101] Bermeo S, Vidal C, Zhou H, Duque G. Lamin A/C Acts as an Essential Factor in Mesenchymal Stem Cell Differentiation Through the Regulation of the Dynamics of the Wnt/beta-Catenin Pathway. *J Cell Biochem* 2015;116:2344-53.
- [102] Dialynas G, Shrestha OK, Ponce JM, et al. Myopathic lamin mutations cause reductive stress and activate the nrf2/keap-1 pathway. *PLoS Genet* 2015;11:e1005231.
- Another signaling pathway activated upon *LMNA* mutation.
- [103] Cattin ME, Muchir A, Bonne G. 'State-of-the-heart' of cardiac laminopathies. *Curr Opin Cardiol* 2013;28:297-304.
- [104] Wilkie GS, Korfali N, Swanson SK, et al. Several novel nuclear envelope transmembrane proteins identified in skeletal muscle have cytoskeletal associations. *Mol Cell Proteomics* 2011;10:27.
- [105] Korfali N, Wilkie GS, Swanson SK, et al. The nuclear envelope proteome differs notably between tissues. *Nucleus* 2012;3:552-564.
- [106] Batrakou DG, de Las Heras JI, Czapiewski R, Mouras R, Schirmer EC. TMEM120A and B: Nuclear Envelope Transmembrane Proteins Important for Adipocyte Differentiation. *PLoS One* 2015;10:e0127712.
- A fat-specific NET found to be involved in genome organization is also critical for adipogenesis. This argues that the function of muscle-specific NETs in muscle genome organization/regulation and differentiation is a general mechanism that could explain any NE disease through the gene regulation hypothesis.
- [107] Farini A, Sitzia C, Cassinelli L, et al. Inositol 1,4,5-trisphosphate (IP3)-dependent Ca²⁺ signaling mediates delayed myogenesis in Duchenne muscular dystrophy fetal muscle. *Development* 2016;143:658-69.
- [108] Cully TR, Launikonis BS. Leaky ryanodine receptors delay the activation of store overload-induced Ca²⁺ release, a mechanism underlying malignant hyperthermia-like events in dystrophic muscle. *Am J Physiol Cell Physiol* 2016;310:C673-80.
- As ryanodine receptors have been found now in the NE, this argues for potential functions in Ca(2+) release in both NE-linked myopathies and potential NE involvement in considered non-NE myopathies.

- [109] Zhao Y, Ogawa H, Yonekura S, et al. Functional analysis of SERCA1b, a highly expressed SERCA1 variant in myotonic dystrophy type 1 muscle. *Biochim Biophys Acta* 2015;1852:2042-7.
- The effect of preferred expression of a SERCA1 splice variant in DM2 on Ca(2+) uptake is shown.
- [110] Michel LY, Hoenderop JG, Bindels RJ. Calpain-3-mediated regulation of the Na(+)-Ca(2)(+) exchanger isoform 3. *Pflugers Arch* 2016;468:243-55.
- [111] Kelkar P, Walter A, Papadopoulos S, et al. Nesprin-2 mediated nuclear trafficking and its clinical implications. *Nucleus* 2015;6:479-89.
- [112] Kramerova I, Ermolova N, Eskin A, et al. Failure to up-regulate transcription of genes necessary for muscle adaptation underlies limb girdle muscular dystrophy 2A (calpainopathy). *Hum Mol Genet* 2016.
- Link between LGMD2A and regulation of gene expression that could further link it to lamin-linked forms and other NE diseases based on the gene regulation hypothesis. Note that calpain was also identified in NE proteomics datasets.
- [113] Smith FJ, Eady RA, Leigh IM, et al. Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. *Nat Genet* 1996;13:450-7.
- [114] Staszewska I, Fischer I, Wiche G. Plectin isoform 1-dependent nuclear docking of desmin networks affects myonuclear architecture and expression of mechanotransducers. *Hum Mol Genet* 2015;24:7373-89.
- Determination of plectin involvement in nuclear anchoring and mechanotransduction.
- [115] Schindler RF, Scotton C, Zhang J, et al. POPDC1S201F causes muscular dystrophy and arrhythmia by affecting protein trafficking. *J Clin Invest* 2016;126:239-53.
- Mutations POPDC1, a protein also identified in the NE by proteomics, cause muscular dystrophy.
- [116] Jeong K, Kwon H, Lee J, Jang D, Pak Y. Insulin-response epigenetic activation of Egr-1 and JunB genes at the nuclear periphery by A-type lamin-associated pY19-Caveolin-2 in the inner nuclear membrane. *Nucleic Acids Res* 2015;43:3114-27.
- Caveolin has an important function in the nucleus. This supports the idea that other myopathies may also have NE links.
- [117] Hetzer M, Meyer HH, Walther TC, Bilbao-Cortes D, Warren G, Mattaj IW. Distinct AAA-ATPase p97 complexes function in discrete steps of nuclear assembly. *Nat Cell Biol* 2001;3:1086-91.
- [118] Senderek J, Garvey SM, Krieger M, et al. Autosomal-dominant distal myopathy associated with a recurrent missense mutation in the gene encoding the nuclear matrix protein, matrin 3. *Am J Hum Genet* 2009;84:511-8.
- [119] Depreux FF, Puckelwartz MJ, Augustynowicz A, et al. Disruption of the lamin A and matrin-3 interaction by myopathic LMNA mutations. *Hum Mol Genet* 2015;24:4284-95.
- Linking of other myopathy-associated proteins historically not thought to have NE associations to NE proteins and NE-linked disease.
- [120] Fuentes-Mera L, Rodriguez-Munoz R, Gonzalez-Ramirez R, et al. Characterization of a novel Dp71 dystrophin-associated protein complex (DAPC) present in the nucleus of HeLa cells: members of the nuclear DAPC associate with the nuclear matrix. *Exp Cell Res* 2006;312:3023-35.
- [121] Aguilar A, Wagstaff KM, Suarez-Sanchez R, Zinker S, Jans DA, Cisneros B. Nuclear localization of the dystrophin-associated protein alpha-dystrobrevin through importin alpha2/beta1 is critical for interaction with the nuclear lamina/maintenance of nuclear integrity. *Faseb J* 2015;29:1842-58.
- Linking of other myopathy-associated proteins historically not thought to have NE associations to the NE.

[122] Chaumet A, Wright GD, Seet SH, Tham KM, Gounko NV, Bard F. Nuclear envelope-associated endosomes deliver surface proteins to the nucleus. *Nat Commun* 2015;6:8218.

■ ■ This paper shows a pathway for delivery of surface proteins previously linked to non-NE myopathies to the nucleus.

Figure Legends

Figure 1. Schematic representation of the nuclear envelope. ONM: outer nuclear membrane, INM: inner nuclear membrane. The LINC complex consists of certain nesprin isoforms in the ONM and SUN proteins in the INM. Additional proteins in the INM are displayed.

Figure 2. What is the underlying cause of NE-linked myopathies? Scientists have gained evidence for many fundamentally distinct mechanisms that could underlie the pathologies of NE-linked myopathies. The jury is still out on whether this reflects multiple independent molecular mechanisms that can cause disease or if they are all part of the same interconnected mechanism. Links between mechanical signal transduction, signaling pathways and gene regulation described here could all be different ways of looking at the same integrated function.

Table 1A: Disease associated nuclear envelope transmembrane proteins

Gene name	Protein name	Associated disease	Phenotype MIM number
VMAA21	VMAA21 vesicular H ⁺ -ATPase homolog	Myopathy, X-linked, with inclusive autophagy	310440
DTNA	Dystrobrevin, alpha	Left ventricular noncompaction 1	604169
RYR1	Ryanodine receptor 1	Central core disease of muscle	317009
		Long QT syndrome	145600
		Malignant hyperthermia susceptibility 1	255320
		Mitochondrial myopathy with external ophthalmoplegia	221300
WFS1	Wolfram syndrome 1 (wolframin)	Wolfram syndrome	600965
		Deafness, autosomal dominant 6/14/38	614296
		Wolfram like syndrome	213080
CHRNA4	Cyclin 144	ItaiItai syndrome	613495
MS4A1	Membrane spanning 4-domains, subfamily A, member 1	Immunodeficiency, common variable, 5	613506
IBRCB1	Leucine rich repeat containing B family, member A	Agammaglobulinemia 5	612244
ABC81	ATP binding cassette, sub-family B (MDR/TAP), member 1	Inflammatory bowel disease 13	211880
EGFR	Epidermal growth factor receptor	Adenocarcinoma of lung, non-small cell lung cancer	610505
		Inflammatory skin and bowel disease, neonatal, 2	607706
ALG2	ALG2, alpha 1, 3/1, 6-mannosyltransferase	Congenital disorder of glycosylation, type II	616228
		Myasthenic syndrome, congenital, 14, with tubular aggregates	167250
SCD1A1	Scavenger 1	Froctosylated dementia and/or amyotrophic lateral sclerosis 1	614337
SLC25A22	Solute carrier family 25	Epileptic encephalopathy, early infantile, 3	609304
MAGT1	Magnesium transporter 1	Immunodeficiency with magnesium defect, Epstein-Barr virus infection and neoplasia	300853
CRELD1	Cysteine-rich with EGF-like domains 1	Atrioventricular septal defect, partial, with heterotaxy syndrome	606317
TMEM70	Transmembrane protein 70	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2	614067
CDSD2	CDGSH from sulfur domain 2	Wolfram syndrome 2	604928
ERLIN2	ER lipid raft associated 2	Spastic paraplegia 18, autosomal recessive	611325
TMEM43	Transmembrane protein 43	Arrhythmogenic right ventricular dysplasia 5	604400
		Emery-Dreifuss muscular dystrophy 7	614302
LBR	Lamin B receptor	HFA skeletal dysplasia	215140
		Polger-Huet anomaly	108400
		Reynolds syndrome	613471
TMPO (LAP2)	Thymopoietin	Cardiomyopathy, dilated, 11	613740
EMD	Emerin	Emery-Dreifuss muscular dystrophy 1	310300
LEM3 (LMAN2)	LEM domain containing 3	Buschke-Olendorf syndrome	166700
		Meloreostosis with osteopetrosis	155950
SYNE1	Nesprin 1	Spinocerebellar ataxia 8	610743
		Emery-Dreifuss muscular dystrophy 4	612998
SYNE2	Nesprin 2	Emery-Dreifuss muscular dystrophy 5	612999
		Muscular dystrophy with rigid spine, contractures of hand joints and cardiomyopathy	
TMEM43 (LAP1)	Tornin A interacting protein 1	Deafness 76	615540
SUN4	SUN1	Emery-Dreifuss muscular dystrophy	
SUN2	SUN2	Emery-Dreifuss muscular dystrophy	
TMEM173 (STUG)	Transmembrane protein 173	STING associated vasculopathy, infantile onset	615334
TMEM126A	Transmembrane protein 126A	Optic atrophy 7	613983
IFPR2	Inositol 1,4,5-trisphosphate receptor, type 2	Anhidrosis, isolated, with normal sweat glands	106190
SLC9A1	NHE-1, solute carrier family 9, isoform A1	Lichtenstein-Knorr syndrome	616291

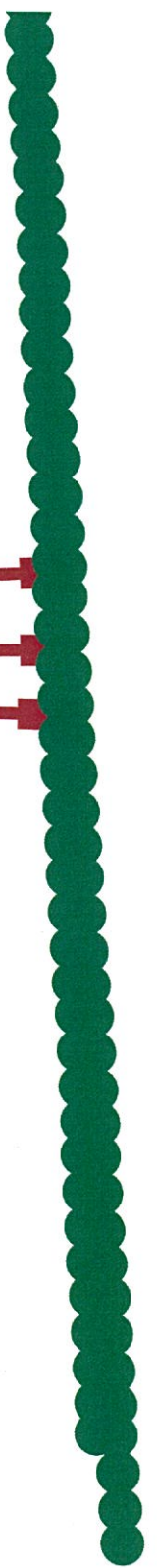
Table 1B: Disease associated lamins and non transmembrane interacting proteins

Gene name	Protein name	Associated disease	Phenotype MIM number
LMNA	Lamin A	Emery-Dreifuss muscular dystrophy 2, AD	181350
		Emery-Dreifuss muscular dystrophy 3, AR	610516
		Muscular dystrophy, congenital	613205
		Muscular dystrophy, limb-girdle, type 1B	259001
		Cardiomyopathy, dilated, 1A	115200
		Lipodystrophy, familial partial, 2	151660
		Charcot-Marie-Tooth disease, type 1B1	805588
		Heart-hand syndrome, Slovenian type	610140
		Maloid syndrome	212112
		Hulkleson-Gilford progeria	176470
		Mandibuloacral dysplasia	244370
		Restrictive dermopathy, lethal	275210
		LMNB1	Lamin B1
LMNB2	Lamin B2	Lipodystrophy, partial, acquired, susceptibility to	608709
		Epilepsy, progressive myoclonic, 9	616540
BAF1	Barrier to autointegration factor 1	Nestor-Guillermo progeria syndrome	614008
ZMPSTE24	Zinc metalloproteinase STE24	Mandibuloacral dysplasia with type B lipodystrophy	608612
		Restrictive dermopathy, lethal	275210

Table 2: Limb girdle muscular dystrophy and Bethlem myopathy associated protein found in muscle nuclear env

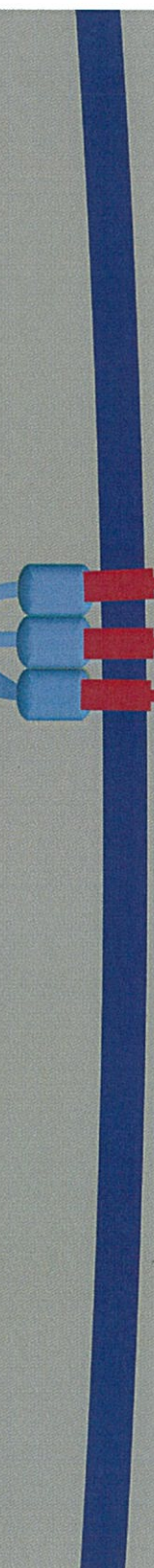
Gene name	Description	Linked disease	TMHMM-prediction	NES: SRs
<i>MYO7</i>	Myotilin	LGMD1A	0	INF
<i>LMNA</i>	Lamin A	LGMD1B; EDMD2/3	0	INF
<i>CAV3</i>	Caveolin 3	LGMD1C	1	0.3
<i>DNAJB6</i>	DnaJ (Hsp40) homolog, subfamily B, member 6	LGMD1D	0	1.1
<i>DES</i>	Desmin	LGMD1E	0	INF
<i>DYSF</i>	Dysferlin	LGMD2B	1	0.1
<i>SGCA</i>	Alpha-sarcoglycan	LGMD2D	1	0.7
<i>SGCB</i>	Beta-sarcoglycan	LGMD2E	1	3.0
<i>SGCD</i>	Delta-sarcoglycan	LGMD2F	1	4.5
<i>SGCG</i>	Gamma-sarcoglycan	LGMD2C	1	2.6
<i>TTN</i>	Titin	LGMD2J	0	INF
<i>POMT2</i>	Protein O-mannosyl-transferase 2	LGMD2N	10	1.1
<i>PLEC1</i>	Plectin 1	LGMD2Q	0	47.8
<i>COL6A1</i>	Collagen, type VI, alpha 1	BTHLM1	0	2.9
<i>COL6A2</i>	Collagen, type VI, alpha 2	BTHLM1	0	3.3
<i>COL6A3</i>	Collagen, type VI, alpha 3	BTHLM1	0	3.0
<i>BVES</i>	Blood vessel epicardial substance /POPC1	LGMD2X	3	3.1

Cyto-
skeleton



Cytoplasm

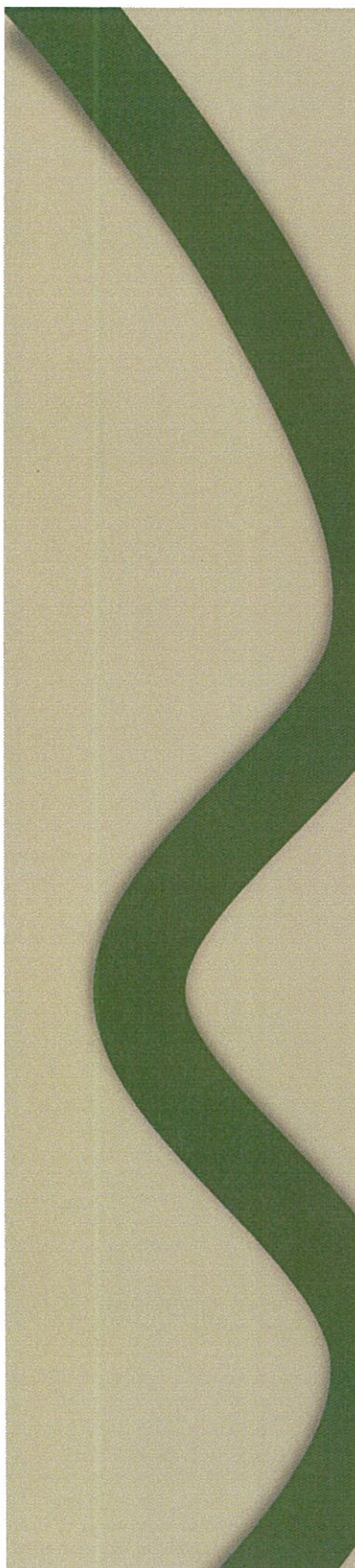
ONM



INM
Lamina



Chromatin



Lumen | Nucleoplasm

