The increasing relevance of nuclear envelope myopathies

The Increasing Relevance of Nuclear Envelope Myopathies

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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, dermopathies, 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], dermopathy [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 LAP2β [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 LAP2β 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 LAP2β, 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 SUN1η 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 TGFβ pathways, [94]), MAN1 (Smad/BMP/TGFβ-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 Ca^{2+} 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 Ca^{2+} release and Ca^{2+}/calmodulin signaling, resulting in a failure to transmit loading-induced Ca^{2+} 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 AΔ303, 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.

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Conflicts of interest:

There are no conflicts of interest.

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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

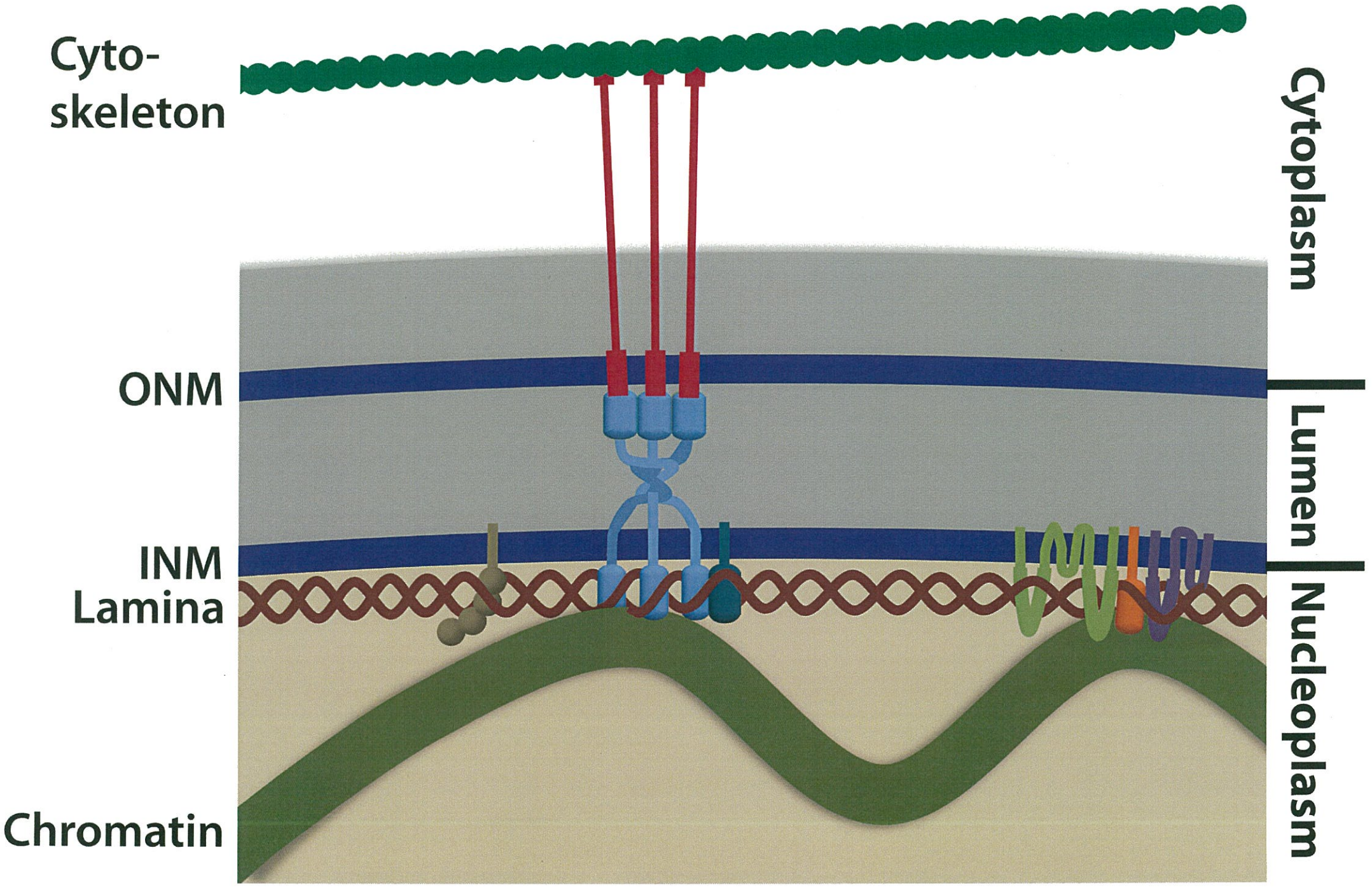
Gene name	Protein name	Associated disease	Phenotype MIM number
VMA21	VMA21 vacuolar H+-ATPase homolog	Myopathy, X-linked, with excessive autophagy	310440
DTNA	Dystrobrevin, alpha	Left ventricular noncompaction 1	604169
RYR1	Ryanodine receptor 1	Central core disease of muscle	117000
		King Denborough syndrome, Malignant hyperthermia susceptibility 1	145600
		Minicore myopathy with external ophthalmoplegia	255320
WFS1	Wolfram syndrome 1 (wolframin)	Wolfram syndrome	222300
		Deafness, autosomal dominant 6/14/38	600965
		Wolfram-like syndrome	614296
CHNK1	Cyclin M4	Jalili syndrome	217080
MS4A1	Membrane-spanning 4-domains, subfamily A, member 1	Immunodeficiency, common variable, 5	613495
LRRC8A	Leucine rich repeat containing 8 family, member A	Agammaglobulinemia 5	613506
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Inflammatory bowel disease 13	612244
EGFR	Epidermal growth factor receptor	Adenocarcinoma of lung, nonsmall cell lung cancer	211980
		Inflammatory skin and bowel disease, neonatal, 2	616069
ALG2	ALG2, alpha-1,3/1,6-mannosyltransferase	Congenital disorder of glycosylation, type Ii	607906
		Myasthenic syndrome, congenital, 14, with tubular aggregates	616228
SQSTM1	Sequestosome 1	Paget disease of bone	167250
		Frontotemporal dementia and/or amyotrophic lateral sclerosis 3	616437
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	606217
TMEM70	Transmembrane protein 70	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2	614052
CISD2	CDGSH iron sulfur domain 2	Wolfram syndrome 2	604928
ERLIN2	ER lipid raft associated 2	Spastic paraplegia 18, autosomal recessive	611225
TMEM43	Transmembrane protein 43	Arrhythmogenic right ventricular dysplasia 5	604400
		Emery-Dreifuss muscular dystrophy 7	614302
LBR	Lamin B receptor	HEM skeletal dysplasia	215140
		Pelger-Huet anomaly	169400
		Reynolds syndrome	613471
TMPO (LAP2)	Thymopoietin	Cardiomyopathy, dilated, 1T	613740
EMD	Emerin	Emery-Dreifuss muscular dystrophy 1	310300
LEMD3 (MAN1)	LEM domain containing 3	Buschke-Ollendorff syndrome	166700
		Melorheostosis with osteopoikilosis	155950
SYNE1	Nesprin 1	Spinocerebellar ataxia 8	610743
		Emery-Dreifuss muscular dystrophy 4	612998
SYNE2	Nesprin 2	Emery-Dreifuss muscular dystrophy 5	612999
TOR1AIP1 (LAP1)	Torsin A-interacting protein 1	Muscular dystrophy with rigid spine, contractures of hand joints and cardiomyopathy	
SYNE4	Nesprin 4	Deafness 76	615540
SUN1	SUN1	Emery-Dreifuss muscular dystrophy	
SUN2	SUN2	Emery-Dreifuss muscular dystrophy	
TMEM173	Transmembrane protein 173 (STING)	STING-associated vasculopathy, infantile-onset	615934
TMEM126A	Transmembrane protein 126A	Optic atrophy 7	612989
ITPR2	Inositol 1,4,5-triphosphate 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	615516
		Muscular dystrophy, congenital	613205
		Muscular dystrophy, limb-girdle, type 1B	159001
		Cardiomyopathy, dilated, 1A	115200
		Lipodystrophy, familial partial, 2	151660
		Charcot-Marie-Tooth disease, type 2B1	605588
		Heart-hand syndrome, Slovenian type	610140
		Mandibuloacral dysplasia	248370
		Hutchinson-Gilford progeria	176670
		Restrictive dermopathy, lethal	275210
LMNB1	Lamin B1	Leukodystrophy, adult-onset	169500
LMNB2	Lamin B2	Lipodystrophy, partial, acquired, susceptibility to	608709
		Epilepsy, progressive myoclonic, 9	616540
BANF1	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
MYOT	Myotilin	LGMD1A	0	INF
LMNA	Lamin A	LGMD1B; EDMD2/3	0	INF
CAV3	Caveolin 3	LGMD1C	1	0.3
DNAJB6	DnaJ (Hsp40) homolog, subfamily B, member 6	LGMD1D	0	1.1
DES	Desmin	LGMD1E	0	INF
DYSF	Dysferlin	LGMD2B	1	0.1
SGCA	Alpha-sarcoglycan	LGMD2D	1	0.7
SGCB	Beta-sarcoglycan	LGMD2E	1	3.0
SGCD	Delta-sarcoglycan	LGMD2F	1	4.5
SGCG	Gamma-sarcoglycan	LGMD2C	1	2.6
TTN	Titin	LGMD2J	0	INF
POMT2	Protein O-mannosyl-transferase 2	LGMD2N	10	1.1
PLEC1	Plectin 1	LGMD2Q	0	47.8
COL6A1	Collagen, type VI, alpha 1	BTHLM1	0	2.9
COL6A2	Collagen, type VI, alpha 2	BTHLM1	0	3.3
COL6A3	Collagen, type VI, alpha 3	BTHLM1	0	3.0
BVES	Blood vessel epicardial substance /POPDC1	LGMD2X	3	3.1


Cyto-
skeleton
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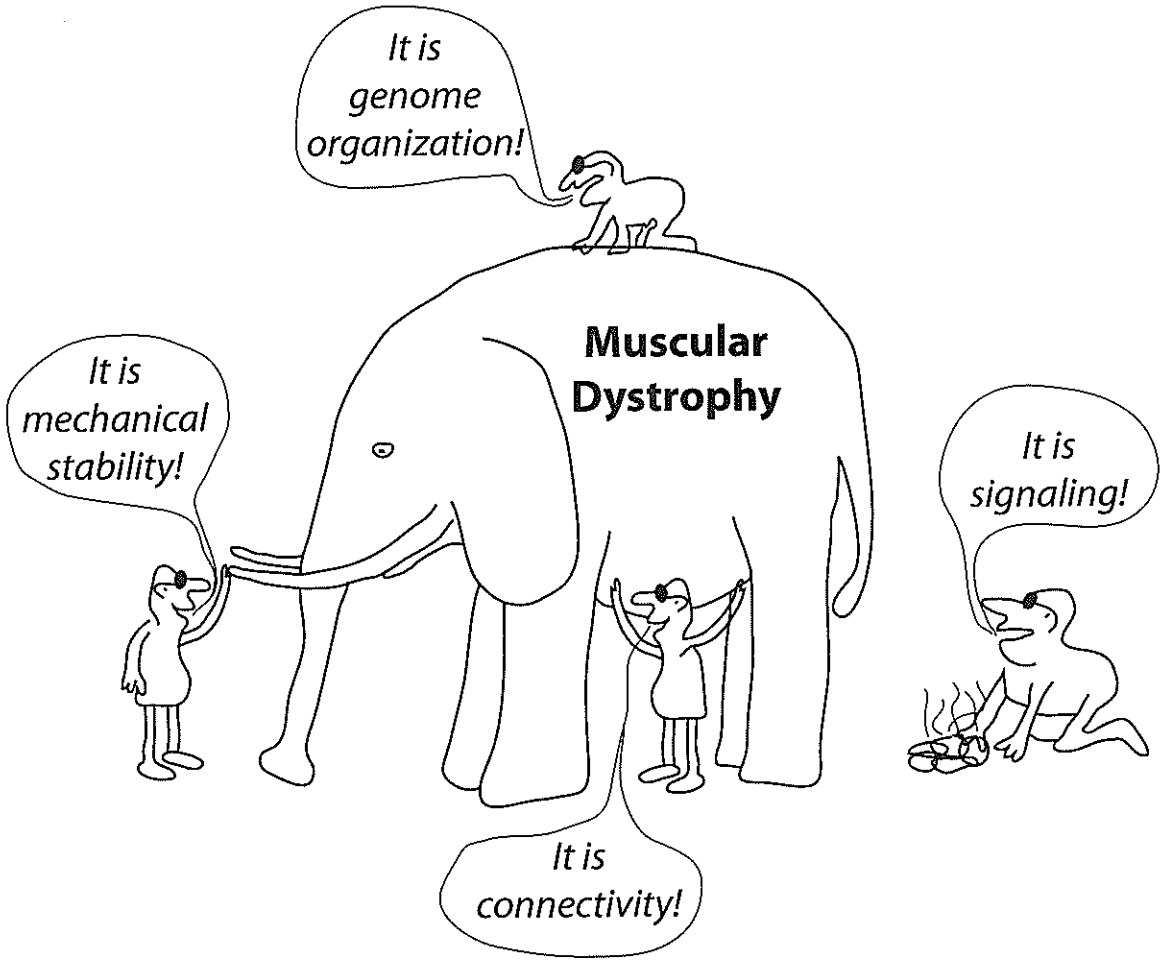
Lamina
Chromatin
Cytoplasm
Lumen
Nucleoplasm


It is genome organization!
Muscular Dystrophy
It is mechanical stability!
It is signaling!
It is connectivity!