Nuclear Envelopathies—Raising the Nuclear Veil

RAZ SOMECH, SIGAL SHAKLAI, NINETTE AMARIGLIO, GIDEON REHAVI, AND
AMOS J. SIMON

Sheba Cancer Research Center, Institute of Hematology, The Chaim Sheba Medical Center and Sackler School of Medicine, Tel-Aviv University, Israel [R.S., S.S., N.A., G.R., A.J.S.], Dana Children's Hospital, Tel Aviv Sourasky Medical Center, and Sackler School of Medicine, Tel-Aviv University, Israel [R.S.]

ABSTRACT

The nuclear envelope separates the chromosomes from cytoplasm in eukaryotic cells and consists of three main domains: inner and outer nuclear membranes and nuclear pore complexes. The inner nuclear membrane maintains close associations with the underlying chromatin and nuclear lamina. For many years, the nuclear envelope was thought to function mainly as an architectural stabilizer of the nucleus, participating in assembly and disassembly processes during mitosis. However, recent findings demonstrate that nuclear envelope proteins are involved in fundamental nuclear functions, such as gene transcription and DNA replication, and that inherited or *de novo* mutated proteins cause human diseases, termed “nuclear envelopathies.” These findings emphasize the importance of understanding the functions of this cellular domain, in both physiologic and pathologic states. To date, mutations in the genes encoding the nuclear envelope proteins emerin, MAN1, lamin A/C, and lamin B receptor were found to cause nuclear envelopathies. The diseases that are caused by mutations in *LMNA* gene are collectively called “laminopathies.” Nuclear envelopathies have diverse clinical phenotypes, ranging from cardiac and skeletal myopathies to partial lipodystrophy, peripheral neuropathy, and premature aging. This raises the question of how do such ubiquitously ex-

pressed proteins give rise to tissue-specific disease phenotypes. One possible explanation is the involvement of nuclear envelope proteins in the regulation of gene transcription, a novel mechanism that has been the focus of research in our lab in recent years. In this review, we describe recent discoveries in the field of nuclear envelopathies and discuss current proposed pathophysiological mechanisms underlying these diseases. (*Pediatr Res* 57: 8R–15R, 2005)

Abbreviations

BAF, barrier-to-autointegration factor
CMT, Charcot-Marie-Tooth
EDMD, Emery-Dreifuss muscular dystrophy
ER, endoplasmic reticulum
GCL, germ-cell-less
HGPS, Hutchinson-Gilford progeria syndrome
INM, inner nuclear membrane
LBR, lamin B receptor
LEM, LAP2 emerin MAN1
NE, nuclear envelope
ONM, outer nuclear membrane
RD, restrictive dermatopathy

The NE forms the boundaries between the chromosomes and the cytoplasm in eukaryotic cells. Its three main components are the INM, the ONM, which is contiguous with the rough ER, and the nuclear pore complexes (1,2) The nuclear lamins polymerize to form a fibrous structure found on the inner surface of the nuclear membrane. This appears as a thin (20–50 nm), stable yet dynamic protein meshwork that maintains extensive interactions with both INM-specific integral membrane proteins and chromatin (3). Nuclear lamins and their associated INM proteins constitute the “nuclear lamina.” At least 18–20 different proteins (including splice variants) from

several species have been described (4). Most of these proteins have large nucleoplasmic domains shown to interact with lamins and/or chromatin. A subgroup of INM proteins named the “LEM domain” group share a conserved 43 residue motif that is exposed to the nucleoplasm. The term “LEM” stands for Lap2 (lamina associated polypeptide) Emerin, and MAN1, although additional LEM domain proteins such as Nesprin, Otefin, and Lem-3 have been recognized (5). The conserved motif suggests that these proteins share a common function and indeed, the LEM domain is known to interact with BAF, a chromatin-associated protein that cross-bridges DNA molecules and prevents viral autointegration (6). (See details in Fig. 1.)

The lamins, type-V intermediate filaments, are major components of the nuclear lamina. Similar to other intermediate filaments, the lamins have a short N-terminal head domain followed by an α -helical rod domain and a long globular tail domain. Two major lamin classes have been defined: type A and type B, which differ in their biochemical and structural

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Correspondence: Amos J. Simon, Ph.D., Sheba Cancer Research Center, Institute of Hematology, Laboratory of Molecular Hemato-Oncology, Chaim Sheba Medical Center, Tel-Hashomer, 52621, Israel; e-mail: amos.simon@sheba.health.gov.il

G.R. holds the Djerasi Chair for Oncology, Sackler School of Medicine, Tel Aviv University. Some of this work was performed in partial fulfillment of the requirements of the Ph.D. degree of R.S., Sackler School of Medicine, Tel Aviv University.

Figure 1. Schematic diagram of NE dynamic organization and its relationship to euchromatin and heterochromatin. The INM and the ONM of the NE are joined at the nuclear pore complexes (NPCs). Integral INM (green) and their associations with chromatin proteins (blue) are indicated. Lamins A/C (black line) and lamin B (red line) are shown as filaments at the nuclear periphery (lamin A/C, lamin B) and in the nucleoplasm (lamin A/C). The binding of the common chromatin binding LEM domain (yellow circles) of several INM proteins and BAF is shown. The bindings of the transcriptional repressors (purple circle); retinoblastoma (Rb) to lamin A/C and GCL to LAP2 β and Emerin, are shown. The two chromatin states, of gene-active unwrapped euchromatin at the nucleoplasm (A), and of gene-silenced condensed heterochromatin at the vicinity of the NE (B) are illustrated. In the latter state, the specific bindings of LBR to Heterochromatin Protein 1 (HP1) through histones H3/H4, and of LAP2 β to BAF are indicated.

properties, their behavior during mitosis, and pattern of expression. Lamin B is known to interact with some integral NE proteins such as LAP2 β , LBR, and Emerin (1).

A growing body of evidence points to the involvement of the nuclear lamina in various fundamental nuclear activities (7). These include maintaining and integrating cell shape (8–9), anchoring chromatin (10), association with nuclear bodies (11), localization to and function in sites of DNA replication (2,12–14) and mediating transcription (15–18). LAP2 β , an integral membrane splice variant of the LAP2 family of proteins, characterized in our laboratory (19), was found to be involved in both fundamental nuclear activities of DNA replication (12) and transcription (17). We have previously shown that LAP2 β represses the transcriptional activity of various transcription factors and binds specifically to transcriptional repressors at the NE (17). The importance of the nuclear lamina in both physiologic and pathologic states was highlighted by recent discoveries that mutations in NE proteins are responsible for a growing group of diseases termed “nuclear envelopathies” (summarized in Table 1). The clinical phenotype of these diseases is variable, ranging from cardiac and skeletal myopathies and partial lipodystrophy to peripheral neuropathy and premature aging (20). This raises intriguing questions such as how ubiquitously expressed lamina proteins give rise to tissue-specific disease phenotypes and how different mutations in the same gene result in such a multitude of seemingly unrelated diseases (21).

We review here the recent discoveries in the field of nuclear envelopathies and outline the current proposed hypotheses regarding the mechanisms by which mutations in proteins of the nuclear lamina lead to such diverse clinical phenotypes.

THE NUCLEAR ENVELOPATHIES

In 1994, a novel X-linked gene responsible for EDMD was identified and the putative protein product was named emerin (22). Two years later, Manilal *et al.* (23) and Nagano *et al.* (24) showed that emerin is a nuclear membrane protein absent in EDMD patients, and were thus the first to link a NE protein to a human disease. EDMD is characterized by slowly progressing contractures and muscle weakness, wasting of skeletal muscle, and cardiomyopathy with conductive disturbances. Heart block is a frequent cause of death. The most consistent cellular feature of X-linked EDMD is loss of emerin from the nuclear periphery (25). In EDMD patient lymphoblastoid cells, an aberrant NE targeting, and cell cycle-dependent phosphorylation of the mutated emerin was demonstrated (26). In EDMD fibroblasts, increased solubility of lamins and redistribution of lamin C and LAP2 α , but not lamin A, to the nucleoplasm were observed as well (27). To date, more than 70 different mutations distributed throughout the gene encoding Emerin (STA gene) have been recognized, most of them nonsense mutations, although frame-shift and missense mutations have also been reported (28). The majority of the mutations cause early termination of translation and almost complete absence of emerin expression with no localization to the nuclear membrane, although mRNA levels are normal (25). The autosomal-dominant variant of this disease was later linked to chromosome 1q11-q23 that contains the lamin A/C gene (LMNA) (29). Although variability exists between patients with EDMD, the two patterns of inheritance are phenotypically almost indistinguishable (30). Missense is the prominent type of mutation responsible for the autosomal form of EDMD. These mutations result in misfolding of the protein or failure to correctly assemble it, leading to partial or complete loss of protein function. A mouse model for EDMD has been created by knocking out the gene that encodes lamin A/C (31). An emerin knockout mouse has not been created yet. Mice that lack lamin A/C develop severe muscle wasting and contractures similar to EDMD by 3–4 wk and die by 8 wk after birth. The LMNA null mice exhibit tissue-specific alterations to their nuclear envelope integrity and mislocalization of emerin to the ER, suggesting that lamin A/C plays a major role in retaining emerin at the inner membrane. In skeletal and cardiac muscles, the phenotype is manifested as a dystrophic condition related to EDMD (31).

Mutations in the gene encoding lamin A/C have been associated with two other myopathies: autosomal dominant limb-girdle muscular dystrophy (32) and dilated cardiomyopathy with conduction system disease (33). The former is similar to classic EDMD, but the different distribution of muscle involvement with slow progressive pelvic girdle weakness while sparing the lower muscles stamps it as a unique disease. Additionally, contractures and cardiac disturbances tend to occur later in patients with limb-girdle muscular dystrophy (34). Dilated cardiomyopathy associated with conductive system disease was first linked to chromosome 1p1–1q1 (35) but later found to associate with mutations in the lamin A/C gene (1p1–q21 locus). Immuno-electron microscopy in patients with dilated cardiomyopathy with atrioventricular block has

Table 1. *The nuclear envelopathies*

Disease	Form of inheritance	Clinical phenotype	Mutated NE protein	Reference
<i>Emery-Dreifuss muscular dystrophy</i>	X-linked	Slowly progressing contractures and muscle weakness, wasting of skeletal muscle and cardiomyopathy	Emerin	22, 24, 25
<i>Emery-Dreifuss muscular dystrophy</i>	Autosomal dominant	Slowly progressing contractures and muscle weakness, wasting of skeletal muscle and cardiomyopathy	Lamin A/C	29
<i>Limb girdle muscular dystrophy</i>	Autosomal dominant	Slowly progressive pelvic girdle weakness, later development of contractures and cardiac disturbances	Lamin A/C	32, 34
<i>Dilated cardiomyopathy with conduction system disease</i>	Autosomal dominant	Dilated cardiomyopathy	Lamin A/C	33, 36
<i>Charcot-Marie-Tooth</i>	Autosomal recessive	Motor and sensory neuropathy, diabetes	Lamin A/C	37, 38
<i>Mandibuloacral dysplasia</i>	Autosomal dominant	Postnatal growth retardation, craniofacial anomalies, skeletal malformations, mottled cutaneous pigmentation	Lamin A/C	41
<i>Dunnigan-type familial partial lipodystrophy</i>	Autosomal dominant	Subcutaneous fat loss, adipose tissue accumulates (face and neck), insulin resistance and diabetes	Lamin A/C	42, 43
<i>Hutchinson-Gilford progeria syndrome</i>	<i>De novo</i> mutation	Premature aging, dwarfism, alopecia, craniofacial disproportion, delayed tooth formation, aged-looking skin, osteoporosis and joint problems. Early death due to atherosclerosis and cardiovascular disease.	Lamin A/C	47, 52
<i>Atypical Werner's syndrome</i>	Autosomal recessive	Scleroderma-like skin, cataract, subcutaneous calcification, premature arteriosclerosis, diabetes mellitus, prematurely aged facies	Lamin A/C	55
<i>Pelger-Huët anomaly</i>	Autosomal dominant	Hypolobulated neutrophil nuclei, coarse chromatin, varying degrees of developmental delay, epilepsy and skeletal abnormalities	Lamin B receptor	58
<i>Greenberg skeletal dysplasia</i>	Autosomal recessive	Lethal course, fetal hydrops, short limbs, abnormal chondro-osseous calcification	Lamin B receptor	60
<i>Restrictive dermopathy</i>	Autosomal recessive	Early neonatal lethal course. Intrauterine growth retardation, tight and rigid skin with erosions, mineralization defects of the skull, pulmonary hypoplasia.	Lamin A/C	61
<i>Restrictive dermopathy (RD)</i>	Autosomal recessive	Early neonatal lethal course. Intrauterine growth retardation, tight and rigid skin with erosions, mineralization defects of the skull, pulmonary hypoplasia.	ZMPSTE24 (FACE-1)	61

Nuclear envelopathies represent a group of inherited diseases that arise through mutations in genes encoding proteins of the nuclear lamina. In each disease, the form of inheritance, clinical phenotype, the mutated NE protein, and citations are presented.

identified loss of protein expression in the selective compartment of noncycling myocyte nuclei (36).

The CMT disorders comprise a group of clinically and genetically heterogeneous axonal variants of inherited motor and sensory neuropathies. Of them, CMT type 2, the autosomal recessive form of this disease, was associated with defects in LMNA, encoding lamin A/C (37). Disease onset occurs in the second decade of life and involves upper limbs and proximal muscles. The course of the disease can be either rapid (38) or characterized by slow deterioration of muscle strength with increasing disability (39).

Mandibuloacral dysplasia, also named craniomandibular dermatodysostosis, is a rare, progeria-like syndrome, characterized by postnatal growth retardation, craniofacial anomalies, skeletal malformations, and mottled cutaneous pigmentation. Affected cells show abnormal distribution of lamin A/C and a dysmorphic envelope. Although clinically diagnosed 30 y ago (40), it was only recently linked to lamin A after identifying a mutation in the LMNA gene on chromosome 1q21 (41). The

breakthrough in exploring the genetic basis of this disease was made after identification of lamin A/C mutation as the cause for a similar disease, Dunnigan-type familial partial lipodystrophy (42). The latter is characterized by subcutaneous fat loss (from the extremities and gluteal and truncal areas) as well as accumulation of adipose tissue in areas of the face and neck and is always associated with insulin resistance and diabetes (43,44). A genome-wide scan with a set of highly polymorphic short tandem repeats in individuals from five well-characterized pedigrees with Dunnigan-type familial partial lipodystrophy mapped the genetic locus to 1q21–q22 (45). Recently, a new clinical condition characterized by generalized lipoatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy has been linked to a novel mutation in lamins A/C (46).

The recent discovery that the HGPS is caused by a *de novo* mutation in the lamin A gene (47) pointed out the importance of the nuclear envelopathies and may shed light on the normal process of aging (48). This rare genetic disease is characterized

by an appearance of accelerated aging in children. The term *progeria* is derived from Greek, meaning “prematurely old.” It was first described in England in 1886 by Dr. Jonathan Hutchinson (49) and again in 1904 by Dr. Hastings Gilford (50); together, they defined the classic Hutchinson-Gilford phenotype. The syndrome consists of premature aging symptoms such as alopecia, craniofacial disproportion, delayed tooth formation, loose skin, osteoporosis joint problems, and dwarfism. Early death (average life span of about 13 y) due to atherosclerosis and cardiovascular problems is the main hallmark of the disease (51). Eriksson *et al.* (47) showed that most classical cases of HGPS share an identical new, noninherited, single-base substitution (G608G, GGC > GGT), within exon 11. This results in the production of a truncated protein product with deletion of 50 amino acids near the carboxy terminus due to activation of a cryptic splice site. Simultaneously and independently, De Sandre-Giovannoli *et al.* (52) reported that the HGPS represents a novel laminopathy, caused by a single heterozygous splicing mutation in the LMNA gene, leading to a major loss of lamin A expression, intimately associated to nuclear alterations. It was shown recently that cellular aging of HGPS fibroblasts was characterized by a period of hyperproliferation that terminated with a large increase in the rate of apoptosis (53). Mice carrying an autosomal recessive mutation in LMNA display marked reduction in growth rate and early death, indicating that it may serve as a mouse model for progeria and possibly help decipher the molecular and cellular mechanisms involved in aging (54).

Other progeroid-like diseases have also been found to be associated with mutations in LMNA. These include atypical and severe Werner syndromes (diseases without mutations at the WRN helicase locus as apposed to the classic Werner syndrome), Seip syndrome, and atypical HGPS (55,56). Three mutations, A57P, R133L, and L140R, in lamin A/C were described in atypical Werner patients. Indeed, altered morphology of the NE and mislocalization of lamins were observed in histopathology of these patients. Clinically, the patients display a more severe phenotype compared with the typical Werner form (55). R644C, E578V, and T101 mutations were found in cell lines obtained from atypical HGPS, severe Werner syndrome and Seip syndrome patients, respectively (56). Other progeroid-like disease, such as Wiedemann-Rautenstrauch syndrome, have not been found in association with mutations in LMNA, but further research may lead to identification of other NE proteins as responsible for the similar phenotype (57). Exploring LMNA mutations as the basic molecular defect associated with progeroid syndromes helps not only in early patient diagnosis and prenatal genetic consultation but also opens new frontiers in the research of the normal process of aging (47,53).

Pelger-Huët anomaly is associated with a mutation in LBR, an integral protein of the NE (58). LBR is composed of eight transmembrane segments displaying sterol delta (14)-reductase enzymatic activity (59). This autosomal dominant disorder is characterized by hypolobulated neutrophil nuclei with coarse chromatin. Homozygous patients display a more severe form, characterized additionally by varying degrees of developmental delay, epilepsy, and skeletal abnormalities. Interestingly, a

different mutation in LBR, which is inherited recessively, causes Greenberg skeletal dysplasia. This autosomal recessive chondrodysplasia has a lethal course and is characterized by fetal hydrops, short limbs, and abnormal chondro-osseous calcification (60). Identification of mutations at the mouse ichthyosis locus within the lamin B receptor gene provide an animal model for determination of the precise functions of LBR, both in normal and pathologic states (61).

The last discovered and most severe disease among the rapidly growing nuclear envelopathies is RD, also called tight skin contracture syndrome (OMIM 275210) (62). RD is mainly characterized by intrauterine growth retardation, tight and rigid skin with erosions, mineralization defects of the skull, pulmonary hypoplasia, and an early neonatal lethal course. Live-born children usually die within the first week of life. Navarro *et al.* (62) explored nine fetuses/newborns children with RD. Two were found to have a heterozygous splicing mutation in the LMNA gene, leading to the complete or partial loss of exon 11 in mRNA encoding Lamin A and resulting in a truncated Prelamin A protein. In the other seven patients, a unique heterozygous insertion leading to the creation of a premature termination codon was identified in the gene ZMPSTE24, also known as FACE-1 in human. This gene encodes a metalloproteinase specifically involved in the posttranslational processing of Lamin A precursor (62).

PROPOSED MECHANISMS UNDERLYING THE NUCLEAR ENVELOPATHIES

Most nuclear envelopathies can be attributed to mutations occurring in one gene, the LMNA gene, thus are called “laminopathies.” The wide variability in clinical presentation of the LMNA-associated diseases raises some interesting questions. Primarily, how can mutations in the same gene give rise to such a wide spectrum of diseases, and not less intriguing is the mystery of how ubiquitously expressed genes give rise to tissue specific phenotypes. Although some pathophysiological mechanisms, derived from the proposed functions of NE proteins, have been suggested (summarized in Table 2), it seems that these questions have yet to be answered. Some of the commonly accepted mechanisms are reviewed below.

MECHANICAL STRESS

Since A-type lamin is essential for maintaining the architecture and structural integrity of the NE (63), a popular and attractive hypothesis is that development of some nuclear envelopathies is a result of mechanical stress imposed on a fragile nucleus. This is followed by alterations in the transcriptional activation of tissue-specific genes (64). A recent study

Table 2. Proposed mechanisms underlying the pathophysiological of the nuclear envelopathies

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- Nuclear organization
 - Nuclear fragility due to mechanical stress
 - Combination of structural and signaling mechanisms
 - Regulation of transcription
 - Relations to the ER functionality
 - Altering cell cycle and replication
 - Effect on differentiation of stem cell lineages
-

supports this hypothesis: Lammerding *et al.* (65) explored nuclear mechanics and mechanotransduction in lamin A/C-deficient mouse embryo fibroblasts. They first demonstrated that these fibroblasts had misshapen nuclei with ultrastructural damage and that their cytoplasm and nucleus had decreased stiffness. In response to applied mechanical strain, the cells exhibited increased nuclear deformation, defective mechanotransduction, attenuated expression of mechanosensitive genes activated by nuclear factor- κ B and diminished viability.

The mechanotransduction hypothesis might explain pathologies of cardiac and skeletal muscle, as the forces generated during muscle contraction predispose these tissues to breakage of nuclei containing a defective nuclear lamina (66). This hypothesis does not explain pathologies in other tissues such as the abnormal fat distribution seen in lipodystrophy patients and neurologic manifestations in patients with CMT. Because mechanical damage to nuclei cannot provide a single explanation for all of the *LMNA*-associated disorders, alternative or additional mechanisms in the etiology of the nuclear envelopathies have been proposed (4).

Another muscle-specific hypothesis points to Myne-1 (myocyte nuclear envelope, also called nesprin-1 α or Syne-1), a muscle-specific inner NE protein, as a potential culprit. Due to its interaction with lamin A/C (67) and its *in vitro* binding to emerin (68), it may take a part in the distorted cytoskeleton of striated myocytes formed in patients with cardiomyopathy and muscular dystrophy. The location and structure of Myne-1 suggest that it may participate in the migration of myonuclei in myotubes and/or their anchoring at the postsynaptic apparatus and accordingly, in the local organization of the cytoplasm (69).

Thus, it might be suggested that cytoskeletal defects produce myopathies through a combination of structural and signaling mechanisms (70). Although this hypothesis seems reasonable, not much knowledge has been gained during the last year to establish this speculation.

GENE EXPRESSION

Recently, great advances have been achieved in the study of the roles of proteins of the nuclear lamina in the regulation of gene expression. These proteins have been shown to be involved in all levels of transcriptional regulation. From the highest level, that of histone modification and chromatin structure, through direct processes of RNA synthesis and splicing, thus linking mutations in these proteins to disease mechanism.

For example, disruption of lamin organization by insertion of a dominant negative lamin A mutant inhibits RNA polymerase II dependent transcription (16). The LAP2 α -lamin A/C complex has been shown to bind the hypophosphorylated form of the retinoblastoma tumor suppressor protein (pRb), a transcriptional repressor of cell cycle genes (71) and to associate with RNA splicing factors in interphase cells (11).

We have previously shown that LAP2 β , an INM protein, represses the transcriptional activity of the E2F5-DP3 α heterodimer, either alone or together with its binding partner, the transcriptional repressor GCL (17). It was also demonstrated that GCL forms complexes with two other NE proteins: lamin A and the LEM-containing INM protein, emerin (72). Emerin

was found also to bind Btf, a death-promoting transcriptional repressor (18). Wilkinson *et al.* (73) showed that emerin interacts with the splicing-associated factor YT521-B in a physiologically significant manner and has a role in a gene expression model of the pathogenesis of EDMD. Regulation of gene expression occurs also at the level of chromatin structure. Modifications of histone tails effect the structure of chromatin rendering it more (euchromatin) or less (heterochromatin) accessible to the transcriptional machinery. Heterochromatin protein 1 (HP1), a protein involved in heterochromatin structure and position effect silencing, was found to repress the expression of euchromatic genes (74) and to associate dynamically with the NE (75). It interacts with the Lamin B receptor (an integral NE protein) and core histones forming a chromatin silencing complex at the nuclear periphery upon deacetylating conditions (76).

Two groups took the microarray approach to investigate the alterations in global gene expression in fibroblasts obtained from EDMD (77) and HGPS (78) patients. These studies, as well as similar experiments in other nuclear envelopathies, will enable a careful dissection and validation of the defected intracellular pathways in each disease, elucidating disease mechanism and identifying possible therapeutic targets.

The "gene expression" hypothesis is supported by two recent studies showing that impaired nuclear mechanics in lamin A/C-deficient mice leads to alterations in gene expression (65,66). These reports suggest a stepwise process in which mechanically stressed pathogenic cells first develop chromatin and NE damage followed by alterations in the transcriptional activation of tissue specific genes.

REPLICATION AND CELL CYCLE

INM have recently been shown to reside in complexes with proteins of the replication machinery of eukaryotic cells (79). HA95 (a chromatin-associated protein) and the nuclear envelope protein, LAP2 β , mediate a novel chromatin-NE interaction implicated in initiation of DNA replication (12). Proteins of the nuclear lamina have been shown to be involved also in other stages of the cell cycle. Correct localization of emerin and A-type lamins is important for maintaining cell cycle timing (80). Immunofluorescent studies, using the MAb LA-2H10, which recognizes the RNA splicing factor associated intranuclear lamin A speckles, demonstrated the disappearance of these speckles during myoblast differentiation and their reappearance when differentiated myoblast were reactivated to enter the cell cycle (81). The integrity of DNA replication and cell cycle progression could also be affected by malfunction of the ER that serves specialized functions in the cell, including protein synthesis. Since the INM makes contact with the ONM at the nuclear pore complexes and the ONM is contiguous with the rough ER, distortion of the nuclear lamina could affect both structure and function of the ER. Thus, we could speculate that alteration in lipidogenesis, seen in lipodystrophic laminopathies, or aberrant Ca²⁺ release during skeletal and cardiac muscle contraction in muscular dystrophies, are due to such an affected rough ER, which functions as the area for calcium sequestration and the main site for production of cholesterol and fatty acids.

SUMMARY

Mutations in the *LMNA* gene have been identified as causing a wide range of clinical phenotypes, the laminopathies, which are part of the nuclear envelopathies described above. The enigma as to how these different pathologies arise from alterations in the same gene, which is almost ubiquitously expressed in adult cells, is only just starting to be revealed (20). The findings are intriguing, as they link proteins of the nuclear lamina to fundamental cellular functions, such as DNA replication and gene transcription. Distinct functional domains in lamin A/C that are essential for the maintenance and integrity of different cell lineages may give a clue (37). Indeed, familial partial lipodystrophy and mandibuloacral dysplasia laminopathies are caused by mutations at the surface of the lamin A/C globular domain, whereas the muscle laminopathy mutations affect the inside of the globular domain. Another worthwhile speculation stems from the observation that most tissues affected in the nuclear envelopathies are mesenchymal in origin. Thus, mutations in lamins A/C and emerin can selectively affect the differentiation, maintenance, repair, or regulation of cells in the mesenchymal stem cell lineage (82). Opposing this theory is the fact that the progeria and CMT laminopathies are ectodermal in origin, again pointing to the complexity in the pathogenesis of nuclear envelopathies.

A recent interesting proteomic analysis of NE fraction (83) has identified many uncharacterized open reading frame proteins, predicted to be part of the NE. Some of these proteins map within chromosome regions linked to a variety of dystrophies. This leads to the assumption that future research may link proteins of the nuclear lamina to many known pathologic states. Exploring the molecular mechanisms that lead to the development of nuclear envelopathies has become a common interest to both clinical and basic researchers. It not only sheds light on the pathogenesis of this group of diseases, possibly enabling the development of treatment protocols, but also reveals that what was once believed to be a structural organelle is indeed a dynamic participant in fundamental nuclear functions.

Notes added in proof

1. A fourth NE protein and the second LEM domain containing protein was recently assigned to increased bone density disorders, elongating the list of Nuclear Envelopathies. Loss-of-function mutations in *MAN1* (also called *LEMD3*) result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis (84).
2. Similar to the LEM domain containing proteins *LAP2 β* and emerin, *MAN1* was found recently to bind *GCL* as well (85).

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