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Nuclear Lamins: Laminopathies and Their Role in Premature Ageing

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Broers, J. L. V., F. C. S. Ramaekers, G. Bonne, R. Ben Yaou, and C. J. Hutchison. Nuclear Lamins: Laminopathies and Their Role in Premature Ageing. *Physiol Rev* 86: 967–1008, 2006; doi:10.1152/physrev.00047.2005.—It has been demonstrated that nuclear lamins are important proteins in maintaining cellular as well as nuclear integrity, and in maintaining chromatin organization in the nucleus. Moreover, there is growing evidence that lamins play a prominent role in transcriptional control. The family of laminopathies is a fast-growing group of diseases caused by abnormalities in the structure or processing of the lamin A/C (*LMNA*) gene. Mutations or incorrect processing cause more than a dozen different inherited diseases, ranging from striated muscular diseases, via fat- and peripheral nerve cell diseases, to progeria. This broad spectrum of diseases can only be explained if the responsible A-type lamin proteins perform multiple functions in normal cells. This review gives an overview of current knowledge on lamin structure and function and all

known diseases associated with *LMNA* abnormalities. Based on the knowledge of the different functions of A-type lamins and associated proteins, explanations for the observed phenotypes are postulated. It is concluded that lamins seem to be key players in, among others, controlling the process of cellular ageing, since disturbance in lamin protein structure gives rise to several forms of premature ageing.

I. INTRODUCTION

The nucleus is the defining feature of eukaryotic cells and is separated from the cytoplasm by the nuclear envelope (NE). The NE is composed of three distinct elements, i.e., the nuclear membrane, nuclear pore complexes, and the nuclear lamina (132). The nuclear membrane is a double-unit nuclear membrane, in which the outer nuclear membrane (ONM) is continuous with and shares biochemical and functional properties with the endoplasmic reticulum (ER). In contrast, the inner nuclear membrane (INM) is distinct from both the ONM and ER and is defined by a subset of integral membrane proteins, termed nuclear envelope transmembrane proteins (NETs), that are anchored to the INM during interphase (322). The ONM and INM are separated by a luminal space of ~100 nm in width. The nuclear membrane is punctuated by nuclear pore complexes (NPCs), which regulate the passage of macromolecules between the nucleus and the cytoplasm (138). At NPCs the ONM and INM converge at the so-called pore membrane, which again is defined by its own subset of integral membrane proteins (148, 403). Underneath the INM is the nuclear lamina. In the NE of giant amphibian oocyte nuclei (germinal vesicles or GVs), the lamina is made up of a lattice of interwoven intermediate-type filaments that interconnect NPCs (Fig. 1, *A* and *B*) (1). Although their ultrastructure has not been defined in other cell types, the principle components of all nuclear laminae are members of the lamin family of type V intermediate filament (IF) proteins (106, 252).

Recently, interest in the NE has intensified after the discovery that mutations in either proteins of the nuclear membrane or lamins or NPC proteins give rise to a wide range of inherited diseases, collectively termed either nuclear envelopathies if mutations arise in INM or NPC proteins (reviewed in Refs. 45, 274, 346), or laminopathies if mutations arise in lamins (reviewed in Refs. 26, 46, 147, 177). These diseases include striated muscle disorders, partial lipodystrophy syndromes, peripheral neuropathies, progeroid syndromes, and conditions that lead to severe developmental abnormalities and death in utero (reviewed in Ref. 346). In addition to these diseases, changes in the expression patterns of lamins have also been implicated in tumor progression (e.g., Refs. 40, 369). Clearly, the association of NE proteins with such a wide range of diseases implies important functions for these proteins in the normal development and/or maintenance of many different tissue types. Indeed, many NE proteins have differential expression profiles during development

and have been implicated in a range of cellular functions including the maintenance of cellular architecture, apoptosis, DNA replication, and transcription (reviewed in Ref. 175). Importantly, lamins that appear as a prominent rim-like labeling of the nuclear envelope in immunofluorescence (Fig. 1, *C* and *D*) interact with and apparently stabilize several other structural NE proteins, such as emerin (Fig. 1*E*) and nesprins. In addition, the appropriate distribution of nuclear pore complexes in the nuclear membrane is maintained by lamins (175) (Fig. 1*F*). In this review, we attempt to explain the involvement of NE proteins in nuclear envelopathies and laminopathies in the light of more recent knowledge of their cellular functions, and their direct interaction with other nuclear proteins. For clarity, we focus on known interactions with other mammalian nuclear proteins. In addition, we consider how some laminopathies might throw new light on pathological processes that are common features of old age.

II. OVERVIEW OF NUCLEAR ENVELOPE AND LAMINA PROTEINS

While the principle components of the nuclear lamina, the lamins, have been characterized for many years (reviewed in Refs. 175, 358), a more complete characterization of integral membrane proteins of the INM has only recently been undertaken using a proteomic approach (322). Therefore, by definition, understanding of the function of most INM proteins is in its infancy, whereas lamins have both clearly defined and emerging roles. For this reason and because of the fact that the vast majority of the disease-causing mutations fall into the category of laminopathies, our review concentrates on the lamins.

A. The Lamina and the Lamin Family

The nuclear lamina was originally defined in ultrastructural studies as a fibrous component of the nucleus (295), which is detergent and salt resistant (90). Subsequent biochemical and immunohistochemical investigations revealed that the major components of the nuclear lamina from rat liver were polypeptides migrating between 65 and 70 kDa in SDS-polyacrylamide gel electrophoresis that were termed lamins. During mitosis, the lamina is disassembled and the lamin polypeptides behave in two distinct ways: two lamins with relative molecular masses of 70 and 65 kDa (lamins A and C, respec-

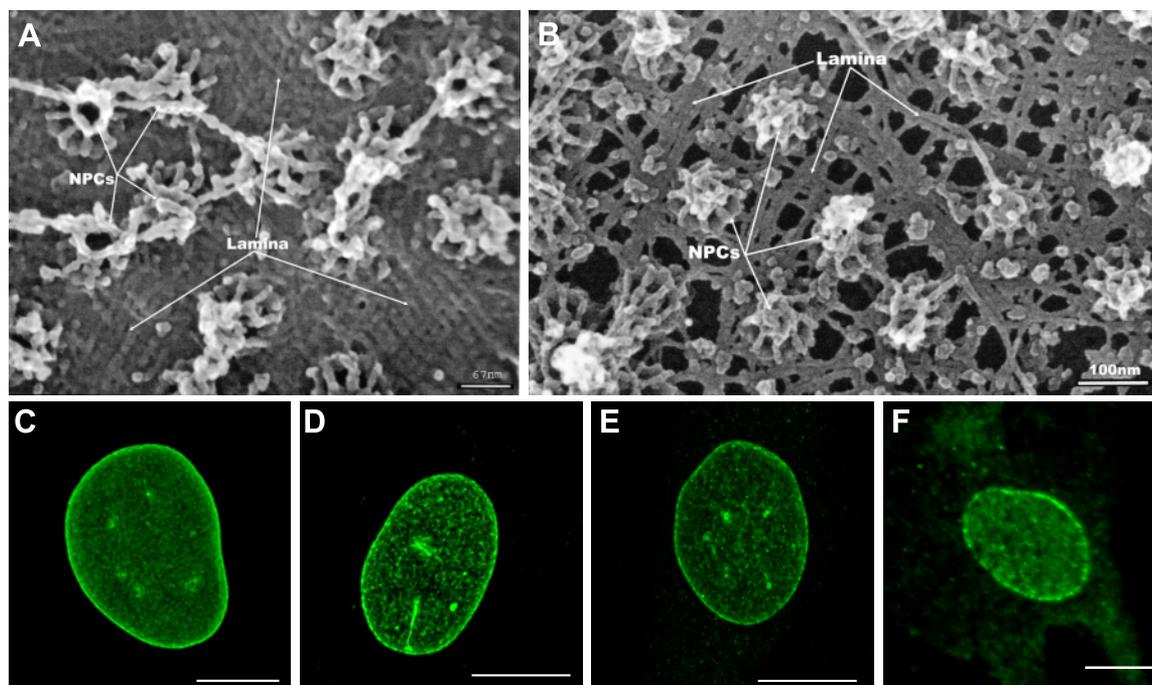


FIG. 1. *A* and *B*: field emission scanning electron micrographs showing lamina organization in *Xenopus* oocyte germinal vesicle (GV) envelopes. Manually isolated oocyte GV envelopes were spread on silicon chips and either extracted with Triton X-100 before fixation (*A*) or fixed directly (*B*), before coating. Lamin filaments can be seen to be extending between nuclear pore complexes (NPCs). In detergent-extracted specimens, the filaments appear stretched, whereas in directly fixed specimens, the filaments can be seen as a square lattice juxtaposed to the membrane. *C–F*: immunofluorescent labeling of human skin fibroblasts with antibodies to lamin A/C (*C*), lamin B1 (*D*), emerin (*E*), and the nuclear pore complex protein p62 (*F*). Fluorescence was recorded by confocal scanning microscopy, followed by image restoration. Note the intense decoration of the nuclear envelope, but also the prominent staining of intranuclear structures.

tively) are freely soluble dimers and are termed A-type lamins. In contrast, two lamins with molecular masses of 67 and 68 kDa (lamin B₁ and B₂) remain associated with membranes and are termed B-type lamins (129, 131). After a detailed investigation of the fine structure of the lamina of *Xenopus* oocyte GVs using freeze drying and metal shadowing, it was clear that the lamina was composed of filaments with the dimensions of intermediate filaments (1). Subsequent cloning and sequencing confirmed that lamins were indeed members of the IF supergene family and were classified as the type V IF family (106, 252).

IF proteins have a well-defined conserved domain structure consisting of a variable NH₂-terminal globular head domain, a central α -helical rod comprising four coiled-coil domains separated by linker regions L1, L12, and L2 (65), and a globular COOH-terminal tail domain (Fig. 2). The coiled-coil domains 1A, 1B, 2A, and 2B are organized around heptad repeats (309). Within coil 1B of the coiled-coil domain, there are 42 additional residues (6 heptads) that are not present in other IF proteins (106, 252). Coiled-coil domains form ropelike structures, and in lamins these domains form dimers of ~50 nm in length (1). The linker regions, interconnecting the coiled-coil regions, are evolutionary highly conserved sequences, suggesting an important role in lamin structure and function (65). At present, no X-ray structures are available for

the three linker regions. For all types of intermediate filaments, L2 seems to have a relatively rigid conformation (284). In contrast, linker L12 seems to be relatively flexible and may serve as a “hinge” between the coiled-coil segments in intermediate filaments (344). Linker L1, the most flexible region in intermediate filaments type I–IV (344), is predicted to be rather rigid in lamins and seems to adopt an α -helical conformation, similar to linker L2 (298).

Compared with other intermediate filaments, the globular head domain of lamins is generally much shorter than in other IF proteins, and this 28-residue head of lamin A (and C) is highly positively charged. The same holds true for the COOH-terminal part of the rod domain, indicating that both regions are important for protein-protein interactions (see below). Recent X-ray crystallog-

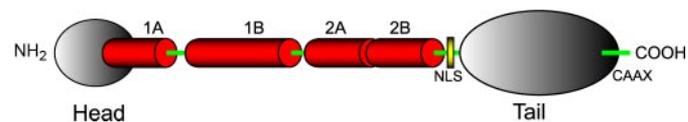


FIG. 2. Schematic structure of lamin proteins. Main characteristics are four central rod domains (1A, B, 2A, B), flanked by a globular head and a globular tail domain. In the globular tail domain, a nuclear localization signal (NLS) can be identified, as well as a CaaX motif, which is absent in lamin C but present in lamin A and in B-type lamins.

raphy (84) and NMR (205) studies have revealed that the globular COOH-terminal domain of lamins (~116 residues long) shows an Ig-like structure. These 116 residues are folded into a β -sandwich of nine β -strands. The core of this globular domain is formed by hydrophobic residues, while most charged residues occur at the surface of the molecule (205), allowing interactions with other (non-lamin) proteins or DNA (354).

Between the COOH-terminal part of the rod domain and the Ig-like domain, lamins contain a nuclear localization signal sequence, not present in other IF proteins (113). Mutations in the nuclear localization signal lead to aberrant assembly of lamins in the cytoplasm (230).

Lamins are the only IF proteins to possess a COOH-terminal CaaX motif (see sect. *uB*) that is the site of posttranslational modifications (206, 389). The number of lamin polypeptides found in different metazoan organisms varies (397). In general, vertebrates express multiple lamins with both germline-specific, embryo-specific, and somatic forms. In contrast, arthropods and invertebrates express only one or two lamins (175). Humans have three distinct lamin genes that encode seven different proteins. The A-type lamins are all alternatively spliced products of a single 12 exon gene located at chromosome 1q21.1–21.3 termed *LMNA* (224, 406). Four different proteins have been described as alternatively spliced products of *LMNA*. Lamins A and C are the major products of *LMNA* in most differentiated cells (106, 252). Lamin C is identical to lamin A up to codon 566, after which it lacks part of exon 10 as well as exons 11 and 12, but possesses five unique basic amino acid residues at its COOH terminus. Lamin A possesses a so-called lamin A specific tail domain from amino acid 567 to 664, which includes a COOH-terminal CaaX motif (106, 252). Lamin A Δ 10 is an alternatively spliced product that lacks all of the residues encoded by exon 10 and has been detected in tumor cell lines as well as several normal cell types (233). Lamin C2 is a germline specific product of *LMNA* (119). Three B-type lamins have been reported in humans thus far. Lamin B₁ is a seemingly unique product of an 11 exon gene *LMNB1* located at chromosome 5q23.3–q31.1 (223). *LMNB2*, located at chromosome 19p13.3 (18), has two alternatively spliced products: lamin B₂, which is expressed in most cells (37), and lamin B₃, which is expressed only in spermatocytes (118).

The A-type and B-type lamins differ not only in their behavior at mitosis, but also in their expression patterns. In avian, amphibian, and mammalian species, lamins B₁ and B₂ are expressed in most cells in both embryos and adult animals (12, 218, 353). Indeed, expression of B-type lamins is essential for nuclear integrity, cell survival, and normal development (153, 219, 226, 383). In contrast to B-type lamins, A-type lamins are differentially expressed, and their appearance in any cell type is normally correlated with differentiation (12, 37, 218, 315). In the mouse,

A-type lamins are dispensable for development, although *Lnma* $-/-$ mice do not survive for more than 8 wk postgestation (360). Similarly, humans lacking functional A-type lamins either die in utero or early after birth (271, 278, 378), while cultured cells lacking lamins A and C can divide quite adequately (153). The contrasting expression patterns of A-type and B-type lamins, together with the finding that B-type lamins are essential for cell survival, have given rise to the notion that B-type lamins are the fundamental building blocks of the nuclear lamina, while A-type lamins have more specialized functions (176).

B. Integral Membrane Proteins of the INM

The first integral membrane proteins (IMPs) of the INM were detected and characterized by their ability to interact with lamins or the lamina (328, 402). More recently, IMPs of the INM have been identified by positional cloning (19), using autoimmune sera (221), through screening for genes with tissue specific expression patterns (154, 420), by homology screening, and by subtractive proteomics (322). To date, some 67 putative nuclear envelope transmembrane proteins (NETs) have been reported in mammals (322), although the vast majority are poorly characterized. For the purposes of the current review, we concentrate on six NETs (Fig. 5) because they are either known to be involved in inherited diseases or because they are likely to be important modifiers of lamin function.

The lamina-associated polypeptides (LAPs) were originally identified through their association with lamina fractions (328). Of these the LAP2 family are the best characterized. There are six alternatively spliced LAP2 isoforms (LAP2 α , β , χ , δ , ϵ , and ϕ), five of which are type II integral membrane proteins sharing a common COOH-terminal transmembrane domain and variable NH₂-terminal nucleoplasmic domains (154). The membrane-associated LAP2 polypeptides primarily bind to B-type lamins (121, 408), are expressed throughout development (209), and are essential for cell survival (153). LAP2 α lacks the transmembrane domain and instead has a long LAP2 α specific COOH-terminal domain. This protein is located in the nucleoplasm instead of the nuclear membrane (78), where it binds to A-type lamins (77).

Emerin was originally identified as a 34-kDa protein encoded by the gene *EMD* (initially called *STA*) located on the human X-chromosome, which when mutated gives rise to the X-linked form of Emery-Dreifuss muscular dystrophy (19). Emerin is also a type II integral membrane protein with an NH₂-terminal nucleoplasmic domain (239, 275). Emerin binds to all lamins but displays a preference for binding to lamin C (92, 381), and its expression patterns in vertebrates closely parallel the expression of A-type lamins (122). Emerin is dispensable for cell survival (153) and normal development (146).

MAN1 is an integral membrane protein with two transmembrane spanning domains and NH₂- and COOH-terminal nucleoplasmic domains (221). MAN1 function is important in early development, where it shares overlapping functions with emerin in lamin binding, chromosome segregation, and cell division that are essential for cell survival (227). These overlapping functions probably explain why emerin is dispensable for development, since these functions can be performed by MAN1. The LAP2, emerin, and MAN1 proteins are apparently related since they all share an ~40 residue conserved domain termed the LEM domain (221). All LEM domain proteins tested so far bind not only to lamins but also the small dimeric protein barrier to autointegration factor (BAF; Refs. 117, 147, 327).

The lamin B receptor (LBR) was originally identified as a lamin B₁ binding protein (402). LBR contains eight putative transmembrane spanning domains (325) and shares structural identity with the sterol reductase multi-gene family (169). LBR is possibly located at the INM through interactions with the chromodomain protein HP1 (411). LBR is essential for fetal development (395), although it is as yet unclear whether this is through a function as a sterol reductase or through its putative role in anchoring chromatin to the NE (234).

The nesprins were first identified as upregulated genes in cardiovascular tissue (420). This family of spectrin repeat proteins turned out to be homologs of proteins independently found to be essential for nuclear migration (5). Nesprin-1 isoforms have been called CPG2, syne-1, myne-1, and Enaptin, whereas nesprin-2 isoforms are also known as syne-2 and NUANCE (5, 66, 142, 260, 292, 418, 420, 421). Nesprins are notable for the giant size of some alternatively spliced variants (they can be >800 kDa). They possess multiple clustered spectrin repeats throughout the core of the protein, NH₂-terminal calponin homology domains, and a conserved COOH-terminal single-pass membrane domain termed a Klarsicht domain (5, 420, 421). Nesprin-1 and nesprin-2 are located in both the INM and ONM, can bind to actin, and are influenced by the actin cytoskeleton (420, 421). Nesprins also bind to lamins A and C and to emerin in vivo and in vitro, and their localization at the NE is dependent on A-type lamin expression (220, 260, 271, 419). Nesprin-3, the most recently discovered member of the nesprin family, does not have an actin binding domain, but instead binds to plectin, a member of the plakin proteins family, which can be associated with intermediate filaments (398).

SUN domain proteins are four human proteins that share a COOH-terminal motif of ~120 residues with the *Caenorhabditis elegans* NE proteins UNC-84 and UNC-83 (165, 236). In *C. elegans* the INM UNC-84 interacts with the ONM UNC-83 within the lumen. Because mutations in UNC-83 or UNC-84 disrupt nuclear migration (236), it is likely that this protein complex is involved in attaching

the NE to the cytoskeleton. Alternatively, the human UNC homologs SUN1 and SUN2 also anchor nesprin-2 to the NE, and therefore, nesprin-2 might be the point of cytoskeleton anchorage (67, 293).

C. Lamin Modifications and Lamin Filament Assembly

Lamins are obligate dimers, although it is still not clear whether lamins form homodimers or heterodimers (147). Recent FRET studies indicate that A-type lamins and lamin B preferentially assemble into homopolymers made up by either A- or B-type lamins (80). Dimerization occurs through in register parallel associations within the coiled coil domains of the central rod region (1). Detailed comparison of the crystal structure of coil 2B of lamins and vimentin revealed significant differences in distribution of charged residues and a different pattern of intra- and interhelical salt bridges (356). These studies suggest that lamins and vimentin might follow different assembly pathways in vivo (356). Lamin dimers are strongly predisposed to forming head-to-tail associations in vitro giving rise to proto-filaments (160, 161, 262). The second order of polymerization is the formation of head-to-tail tetramers, in which a linear association of two lamin dimers is formed by an overlap of the COOH-terminal part of coil 2B and the NH₂-terminal part of coil, mediated by electrostatic interactions between these two coil domains (356). At the next level of polymer organization, lamin protofilaments are predicted to form antiparallel out of register associations, such that individual tetramers have both NH₂-terminal and COOH-terminal overlaps (358). However, only very recently has it been possible to assemble lamins into 10-nm filaments in vitro using the *C. elegans* lamin Ce-lamin (189). Lamins from other species form unstable filaments in vitro and instead aggregate into paracrystalline structures (1, 160, 262).

One reason that it has proven difficult to assemble lamins into 10-nm filaments (as opposed to paracrystals) in vitro is that the highly charged globular head and tail domains interact strongly, and these interactions appear to bias assembly towards head-to-tail associations. Indeed, elimination of the head and, to a lesser extent, tail domains inhibits the formation of head-to-tail polymers (161). Under certain in vitro circumstances, tailless lamins still form lamin polymers (133). However, the Ig tail of lamins does contribute to the formation of a correct lamin polymer, since protein fragments containing this Ig fold inhibit nuclear membrane and lamina assembly and chromatin decondensation in *Xenopus*. A single point mutation within this Ig fold is sufficient to eliminate this dominant negative function of the Ig fold (338).

Posttranslational modification of the head and tail domains of lamins is required to control lamin assembly.

Three types of posttranslational modification have been reported, and at least one of these is central to lamins A/C-related disease.

Lamins undergo phosphorylation during interphase and mitosis. Lamins contain putative cyclin-dependent kinase 1 (cdk1) target sequences in both the globular head domains and globular tail domains. Both of these sequences are close to the ends of the central rod domain (302, 393). Both sequences are phosphorylated by mitotic kinases or cdk1 directly both *in vivo* and *in vitro*, and the phosphorylation of these sites is correlated with lamin filament disassembly (301, 302, 393). Moreover, serine to arginine substitutions within these sites block mitotic disassembly of lamin filaments *in vivo* (158). While complete disassembly of the lamina during mitosis is probably mediated by phosphorylation of the two cdk1 target sequences, there are additional protein kinase target sequences within the lamin tail domain. A protein kinase target sequence within the tail domain of lamin B₁ is the site of modification by nuclear β_{II} protein kinase C (PKC) during interphase and mitosis, and phosphorylation at this site also destabilizes lamin filaments (64). Phosphorylation of a second phosphoacceptor site adjacent to the cdk1 sequence in the head domain, also destabilizes lamin filaments (357). Therefore, phosphorylation of these additional sites during interphase may limit head-to-tail associations between lamin dimers and therefore allows correct lamin filament assembly. It is important in this context that the protein kinase A anchoring protein AKAP149 forms a complex at the INM, which recruits protein phosphatase 1 (PP1). Recruitment of PP1 to the INM is essential for lamina assembly at the end of mitosis (352) as well as maintaining the integrity of the NE during interphase (351). Therefore, it seems likely that a subtle interplay between β_{II} PKC and PP1 ensures the assembly of 10-nm filaments *in vivo*.

Although interplay between β_{II} PKC and PP1 might be important for the assembly of 10-nm filaments, other posttranslational modifications are needed to ensure the assembly of the nuclear lamina at the INM (Fig. 3). All lamins other than lamin C contain a COOH-terminal motif comprising a cysteine, two aliphatic amino acids, and any COOH-terminal amino acid, termed a CaaX box. This motif is the target for a sequence of modifications that lead to isoprenylation and methylation of the COOH-terminal cysteine residue. Addition of a 15-carbon farnesyl isoprenoid to the cysteine occurs initially within the nucleoplasm, and this is followed by proteolytic cleavage of the aaX (10, 98, 136, 342, 389, 401).

After this cleavage, the cysteine residue is modified by methylation (58, 59, 342). Isoprenylation and methylation of the COOH-terminal cysteine residues are both necessary for the localization of lamin A and the B-type lamins to the INM. However, once at the INM, the fates of lamin A and the B-type lamins differ. Lamin A contains an

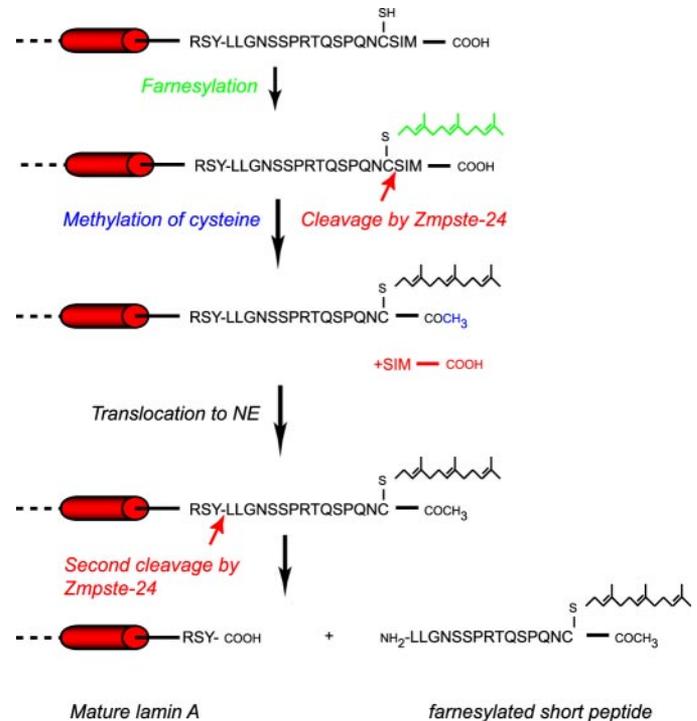


FIG. 3. Processing of prelamins A to mature lamin A involves several steps, including farnesylation at the terminal cysteine site, followed by cleavage of the last three COOH-terminal amino acid residues of the CaaX motif, in this case SIM, probably by Zmpste24; methylation of the cysteine that is COOH terminal after cleavage, followed by a second cleavage of the last 15 amino acids, including the newly added isoprene group. The last cleavage probably takes place during or after incorporation of this molecule into the nuclear lamina. Lamin C is not processed, whereas B-type lamins are farnesylated but not further processed.

additional site for endoprotease cleavage 15 amino acids upstream of the COOH-terminal cysteine residue (10, 196, 389, 396). This site is cleaved at the INM by the ZMPSTE24 zinc metalloproteinase (15, 300). Thus, while B-type lamins remain isoprenylated throughout their life span, lamin A is normally processed from a form referred to as prelamins A (which contains the final 18 amino acids) to mature lamin A (lacking the final 18 amino acids). The loss of the isoprenylated cysteine residue in mature lamin A accounts for its solubility during mitosis, since it is unable to maintain associations with membranes once the lamina is disassembled.

Failure of lamin A maturation has been reported through two independent pathways. With the use of the cholesterol-modifying drug lovastatin, prenylation of lamin A was inhibited and prelamins A accumulated within nucleoplasmic foci (232). In this instance, the product referred to as prelamins A is completely unmodified and maintains its COOH-terminal aaX. In contrast, in ZMPSTE24 $-/-$ mice or cell lines, a partially processed prelamins A product accumulates in the NE (15, 300). This product is presumably isoprenylated and methylated but retains its aaX and is therefore distinct from the product

that accumulates after lovastatin treatment of cells (232). Both nonisoprenylated and isoprenylated prelamin A can be detected with an antibody reagent specific for prelamin A (300, 341). Moreover, the lovastatin-treated prelamin A is predicted to be either unable to associate with the lamina (232) or unstably associated with the lamina (320). In contrast, the ZMPSTE24 $-/-$ prelamin A product is more tightly associated with the lamina (300). For a recent review on prelamin A processing and processing-related diseases, see Reference 415.

While farnesylation and methylation of B-type lamins and prelamin A appear necessary for their targeting to the INM, further interactions with IMPs are needed for lamina filament assembly. LAP2 β has been shown to interact specifically with the rod domain of B-type lamins in vitro (120). Moreover, injection of the lamin binding fragment of LAP2 β into living cells inhibits both lamina assembly and NE growth (408). Incubation of LAP2 peptides with cell-free nuclear assembly systems also inhibits lamina assembly (121). Therefore, it seems that LAP2 β is required for assembly of B-type lamins into a nuclear lamina. The constitution of the nuclear lamina is still a matter of debate. While in *Xenopus* a 10-nm lattice of lamin filaments is visible underneath the nuclear membrane, the lamina in mammalian cells such as fibroblasts seems to be highly variable in thickness and their molecular organization is still undisclosed. It might well be that in addition to filament formation other types of organization, such as paracrystals, also exist (164). While at the lower levels of polymer organization most likely homopolymers rather than heteropolymers are formed (80), it is evident that in the lamina of most cells at least four different molecular structures, consisting of lamin A, lamin C, lamin B1, and lamin B2, interact with each other. At the individual cell level, ratios between expression levels of these proteins appear to vary considerably (Broers, unpublished data). To make analyses of the structure of the lamina even more complicated, it has been shown recently that lamin binding interactions in vitro differ significantly between partners. While a relatively strong binding can exist between lamins A, C, and B1, interaction with lamin B2 appears to be much weaker, while even lamin B2-lamin B2 interactions are weaker than the other combinations. This suggests that the distinctive combination of heterotypic lamin interactions affects the stability of the lamin polymer (323).

How are the A-type lamins then assembled into the lamina? Because B-type lamins are essential and one or more B-type lamins are expressed in all cells, it has been proposed that they are the fundamental building blocks of the lamina, while A-type lamins are added into B-type lamin filaments (176). Four lines of evidence support this view. First, during NE reassembly at telophase, B-type lamins appear in a lamina-like structure before A-type lamins (264). Second, in cell-free nuclear assembly sys-

tems, incorporation of lamin A into the lamina is dependent on the presence of B-type lamins (91). Third, A-type lamins are relatively mobile and can migrate between the lamina and the nucleoplasm, whereas B-type lamins are usually rigidly associated with the lamina (41, 265). The relative dynamic behaviors of lamins during interphase and mitosis may well in part underlie at least some of the pathologies observed in lamins A/C-related disease. Fourth, recent mouse models in which the *Lmna* gene was modified, so that only lamin C is expressed, showed that these transgenic animals have a completely normal development (110). Therefore, we now discuss in detail the dynamic behaviors of lamins and NETs.

III. DYNAMIC BEHAVIOR OF LAMINS AND NUCLEAR ENVELOPE TRANSMEMBRANE PROTEINS

A. Lamina Dynamics in Interphase Cells

While the most obvious localization of lamins during interphase is at the nuclear periphery, a growing number of studies suggest that in interphase cells lamins can be found in nucleoplasmic areas as well. On the basis of the most recent insights, three levels of lamin organization can be distinguished: 1) lamins associated with the nuclear membrane, 2) lamins organized into intranuclear tubules and aggregates, and 3) lamins visible as dispersed (veil-like) structures in the nucleoplasm (Fig. 1). We discuss each of the organizational levels and their (potential) functions.

1. Dynamics of nuclear membrane-associated lamins

The most prominent concentration of lamins is seen at the nucleoplasmic site of the nuclear periphery, where lamins assemble into a meshwork of lamin proteins, called the nuclear lamina as described above (Fig. 1).

The dynamics of the nuclear lamina during interphase have been investigated using fluorescence bleaching techniques of lamin-GFP transfected cells. In fluorescence recovery after photobleaching (FRAP), the speed of recovery from photobleaching in a bleached area is measured. Alternatively, one can measure the amount of fluorescence lost after (repetitive) bleaching in a neighboring region outside of the bleached area. This latter technique is called fluorescence loss in photobleaching (FLIP).

With the use of these techniques, it was deduced that most lamin proteins, organized into the lamina, show a very low turnover. Both lamin A-GFP and lamin B1-GFP are almost completely immobile in the lamina, as deduced from the lack of recovery from photobleaching within hours for lamin A and even within 45 h for lamin B1 (41,

73). However, after bleaching of lamin C-GFP, a considerable decrease of the fluorescent signal in the lamina outside of bleached regions is observed, indicating that lamin C is more mobile in the lamina than lamins A or B1 (39), and as such confirming previous biochemical studies (72, 130). The functional implication of the more dynamic behavior of lamin C within the nuclear lamina is unclear at the moment. Lamin C may act as a vehicle for attaching different regions of (hetero-)chromatin to the nuclear membrane, to inactivate gene expression. Alternatively, lamin C may shuttle between the lamina and the nucleoplasmic lamin pool in response to replication and/or transcription regulation.

2. Dynamics of lamins in intranuclear foci and tubules

There is growing evidence that intranuclear lamin foci as seen by different techniques are native lamin structures, possibly associated with initiation of replication sites (193, 348; see however Ref. 85) or transcriptional complexes (183).

While Bridger et al. (30) reported the presence of A-type lamin foci in dermal fibroblasts during G₁ phase of the cell cycle after a special fixation procedure, Moir et al. (263) showed that in particular lamin B is associated with DNA replication foci in S phase cells. A more recent study indicated that A-type lamins are present in foci of DNA replication surrounding the nucleolus, which contain replication proteins such as p150 and PCNA (193). These foci are established in early G₁ phase and also contain members of the pRb family. Later, in S phase, DNA replication sites distribute to regions located throughout the nucleus. As cells progress through S phase, the association of A-type lamins with replication foci and pRB family members is lost. Studies with mutant lamins suggest that normal lamina assembly is required to establish DNA replication centers (92) and that lamins are essential for the elongation phase of DNA synthesis (348).

Next to the association of lamins with replication foci, other investigators have reported on the concentration of lamins in nuclear areas with increased RNA polymerase II activity, indicative of transcription (347). These authors showed that disruption of normal lamin organization inhibits RNA polymerase II activity, suggesting that lamins are involved in the synthesis of RNA by acting as a scaffold upon which the transcription factors required for RNA polymerase II activation are organized. Jagatheesan et al. (183) and Muralikrishna et al. (272) showed a potential role for A-type lamins in the RNA splicing process. They found the presence of intranuclear A-type lamin foci, which associate with RNA splicing speckles in C2C12 myoblasts and myotubes. Lamin speckles were observed in dividing myoblasts but disappeared early during the course of differentiation in postmitotic

myocytes, and were absent in myotubes and muscle fibers. These results suggest that muscle cell differentiation is accompanied by regulated rearrangements in the organization of the A-type lamins (183, 272). More recent work, however, questions an essential role of lamins A/C in splicing, since mouse *Lmna* ^{-/-} cells still seem to be able to maintain fully functional splicing factor compartments (382). In fact, the specific intranuclear speckles can only be detected using one particular monoclonal antibody and could well represent something other than lamin containing structures (382).

It is likely that at least some of the intranuclear lamin foci seen with immunofluorescence are similar to the intranuclear and transnuclear channels observed after microinjection (115) or vital imaging with GFP-lamin transfected cells (41). These intranuclear channels are visible both after transfection with GFP-tagged A-type lamins or with GFP-lamin B1 (35), but also in normal human fibroblasts using conventional immunofluorescence staining (Figs. 1 and 4). The number of intranuclear channels is highly variable, ranging from zero to tens of channels per cell. Most of these tubules contain membrane lipids as well as nuclear pore complex proteins. A-type lamins, lamin B, emerin, and nuclear pore complex proteins can be immunostained in these channels, indicating that these fully developed nuclear membrane invaginations could serve as transport channels between different cytoplasmic regions (115). In addition, it has been shown that cytoplasmic actin proteins are also present in these structures (187). Vital imaging indicates that these channels can persist for a prolonged period of time and appear to be rather stable, but flexible, similar to the lamins present in the nuclear lamina as seen in three-dimensional imaging in time. Bleaching studies showed that fluorescent GFP-tagged lamin channels are stable with a very low turnover of fluorescent molecules, similar to lamins in the nuclear lamina (41). Although in our studies no correlation with cell cycle state and the presence of nuclear channels was observed, Johnson et al. (187) suggest that the number of channels increases with dedifferentiation. In artificial systems, overexpression of lamins A, B1, or B2, but not lamin C, leads to nuclear membrane growth, which is accompanied by nuclear folding and an increase of nuclear invaginations or so-called intranuclear membrane assemblies. Apparently, the presence of (part of) the CaaX motif in lamins is sufficient to induce nuclear membrane growth (308). Currently, it is unclear whether processed or unprocessed lamin A can cause such a growth. Prufert et al. (308) state that in the model they used, prelamin A was presumably unprocessed, while others could detect increased intranuclear channel formation after transfection with lamin A-GFP, which was demonstrated to be fully processed (41). Similarly, accumulation of progerin, which is partially pro-

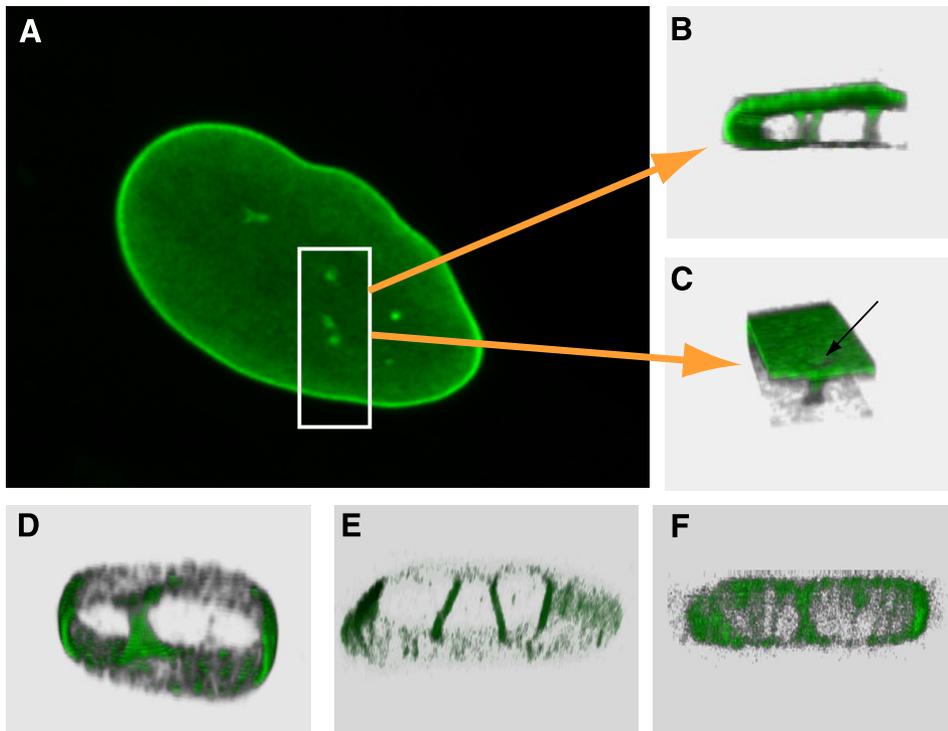


FIG. 4. Demonstration that intra- and transnuclear lamina channels are common structures in normal human fibroblasts. Cells were immunostained, and three-dimensionally reconstructed nuclei were optically sectioned in the outlined area and visualized using three-dimensional imaging software. Note the presence of several intranuclear tubules with a hollow appearance and a funnel-like indentation at the opening of the channel. Immunofluorescence showed the presence of lamin A/C (A–C), as well as lamin B1 (D), emerin (E), and the nuclear pore complex protein p62 (F) in these channels.

cessed mutated prelamin A (see below), causes the formation of intranuclear membrane invaginations (250).

3. Dynamics of nucleoplasmic lamins

Ultrastructural investigations suggest the presence of a dispersed intermediate filament lamin network throughout the nucleus (171, 180, 181). Also, GFP tagged *cdc14b* labeling shows a prominent nuclear network of filaments that begin at the nucleolar periphery and extend to the nuclear envelope, frequently making close connections with nuclear pore complexes (276). The existence of a dispersed, veil-like nucleoplasmic lamin network was suggested after the use of different bleaching techniques, which showed that a considerable fraction of intranuclear lamins, visible as diffuse nucleoplasmic fluorescence, is stably integrated in the nuclear interior (41, 265). Strikingly, a large intercellular variation in fluorescence retainment is observed after lamin C-GFP transfection, which is more pronounced than in lamin A-GFP transfected cells (39). Interaction with other intranuclear structures, including (temporary) chromatin association or binding to nuclear histone proteins, known to show *in vitro* interaction with lamins (139, 361), seems an obvious explanation for this phenomenon. The exact molecular structure of this lamin veil is unknown. The resolution of light microscopy does not allow insight in such structures. While immunoelectron microscopy studies seem to reveal lamin-containing structures, the fixation and permeabilization methods used could promote artifacts. Therefore,

while it has been suggested that lamins can polymerize into intranuclear intermediate filaments (171), a different assembly pattern could be possible. The role of this fine network in cellular processes is unclear so far. It is suggested that these nucleoplasmic lamin filaments provide a scaffold for processes such as transcription and DNA replication (see sect. v). Bleaching studies on cell lines transfected with GFP-lamins, in which mutations similar to those seen in Emery-Dreifuss muscle dystrophy and Dunnigan's type lipodystrophy patients were induced, showed that these mutated lamins do not incorporate properly into a nucleoplasmic veil (36). These findings support the possible importance of A-type lamins in normal DNA functioning.

B. Lamin Dynamics During Mitosis

1. Lamina breakdown

The most dramatic changes in the lamina architecture occur during the process of cell division. At the transition from prophase to prometaphase, the nuclear membrane and the lamina disassemble. For a long time it has been thought that phosphorylation by *cdk1* of, among others, lamin proteins alone is the onset nuclear envelope breakdown (302, 393). However, recently it has been suggested that at the end of prophase microtubules bind to the nuclear membrane via dynein and tear away membrane fragments from the nucleus. As a result, the nuclear envelope becomes partially disrupted, allowing kinases to

enter the nucleus and to phosphorylate lamin molecules, which subsequently become solubilized (8). Although the mechanism of nuclear membrane tearing by microtubules is an intriguing observation, other findings argue against a key role for microtubule tearing in evoking mitosis. First, in cells lacking *cdk1*, microtubules and dynein are normally present, yet no breakdown of the nuclear envelope occurs (210). Second, the lamin (B1) polymers present in interphase cells can resist a much higher tension than the force, which can be created by microtubules pulling the nuclear membrane. Therefore, a combination of phosphorylation and membrane pulling rather than tearing seems to be a logical scenario for the initiation of mitosis. In mammalian cells, the dissociation of A-type lamins from the nuclear lamina starts at early prophase, whereas B-type lamins dissociate only later (128). A-type lamins were suggested to become solubilized and disperse completely into the cytoplasm, while B-type lamin particles remained associated with nuclear membrane structures (129, 280). This view has recently been questioned, and lamin B1-GFP studies suggest that B-type lamins are solubilized at the onset of mitosis (8, 73). However, whether native B-type lamins become detached from the nuclear membrane vesicles during mitosis remains to be proven. The sequence of dissociation of other NE proteins, which is largely dependent on lamina disassembly, is difficult to determine because of the short duration of this particular phase of the cell cycle, and the extensive epitope alterations of proteins resulting from phosphorylation (244).

2. Lamina reassembly

Lamina reassembly commences with the association of LAP2 α and BAF with the ends of chromosomes accompanied by LBR and a small fraction of emerin (151), followed by LAP2 β (76, 151). Some contradictory data exist about the reassembly of B-type lamins, in particular lamin B1, after mitosis. Studies with GFP-tagged human lamin B1 in mitotic cells have shown that this lamin begins associating with the peripheral regions of chromosomes during late anaphase to mid-telophase, suggesting that lamin B1 polymerization is required for both chromatin decondensation and the binding of nuclear membrane precursors during the early stages of normal nuclear envelope assembly (231, 265). However, other studies found that accumulation of lamin B1 around chromatin could only be detected in late telophase/early cytokinesis, a stage when chromatin is already sealed by a pore-containing membrane (39, 73). Starting at telophase, lamin B1 (re)associates with membrane particles, which, however, do not yet surround the chromosomes. This B-type lamin assembly can be seen shortly after LAP2 β is visible around the chromatin (76). Only at late telophase/cytokinesis lamin B1-GFP reassembles into a nuclear membrane structure.

Vital imaging of A-type lamin-GFP transfected cells (41, 265) showed that after metaphase lamina reassembly of all three A-type lamins (lamin A, lamin A Δ 10, and lamin C) does not commence until after cytokinesis. The majority of all three A-type lamin molecules do not move toward the newly formed nucleus until cytokinesis is completed (41), when the bulk of A-type lamins seems to translocate through the newly formed NPC (57). At that stage, the A-type lamins associate very rapidly with the chromatin and the nuclear envelope, since in our studies no GFP signal was any longer visible in the cytoplasm surrounding the chromosomes within 3 min after initiation of lamin-GFP condensation. While vital imaging studies of GFP-lamin distribution cannot exclude that a subpopulation of especially lamin C molecules already concentrates at parts of the chromosome surfaces at late anaphase as suggested previously (76, 107, 407), it is clear that the majority of A-type lamin molecules only reassemble during and after cytokinesis. Because mature lamin A and lamin A Δ 10 have lost their isoprenyl tail after incorporation into the nuclear membrane, reassembly of these proteins after mitosis, along with lamin C, will involve a mechanism that is independent from this isoprenyl group.

IV. FUNCTIONS OF LAMINS IN NUCLEAR AND CELLULAR ARCHITECTURE

As the major structural proteins at the INM, the lamins have important anchorage functions for NETs. Lamins/NET complexes have at least three clearly defined or emerging functions in maintaining cellular architecture. Lamins/NET complexes are important for organizing peripheral chromatin. The lamins also have important functions in positioning NPCs within the NE, and it is now emerging that lamins also have a crucial role in organizing the cytoskeleton. Because lamins appear to have such a central role in organizing so many different architectural elements within the cell, it is widely believed that the lamina is the cellular equivalent of a tensegrity device (a structure that is not unlike a geodesic dome), which is a loadbearing structure that provides resilience and an ability to resist forces of deformation in cells that lack cell walls (reviewed in Ref. 175; see also Refs. 38, 417).

A. Interactions between lamins, NETs, and BAF

The nematode *C. elegans* has provided an important model system for understanding the nature of protein complexes that are orchestrated around lamins. *C. elegans* only expresses a single B-type lamin, Ce-lamin, and this protein can be readily knocked down using RNA interference (RNAi) (226). While RNAi knockdown of Ce-lamin is generally embryonic lethal, sufficient development occurs to evaluate the anchorage functions of this protein.

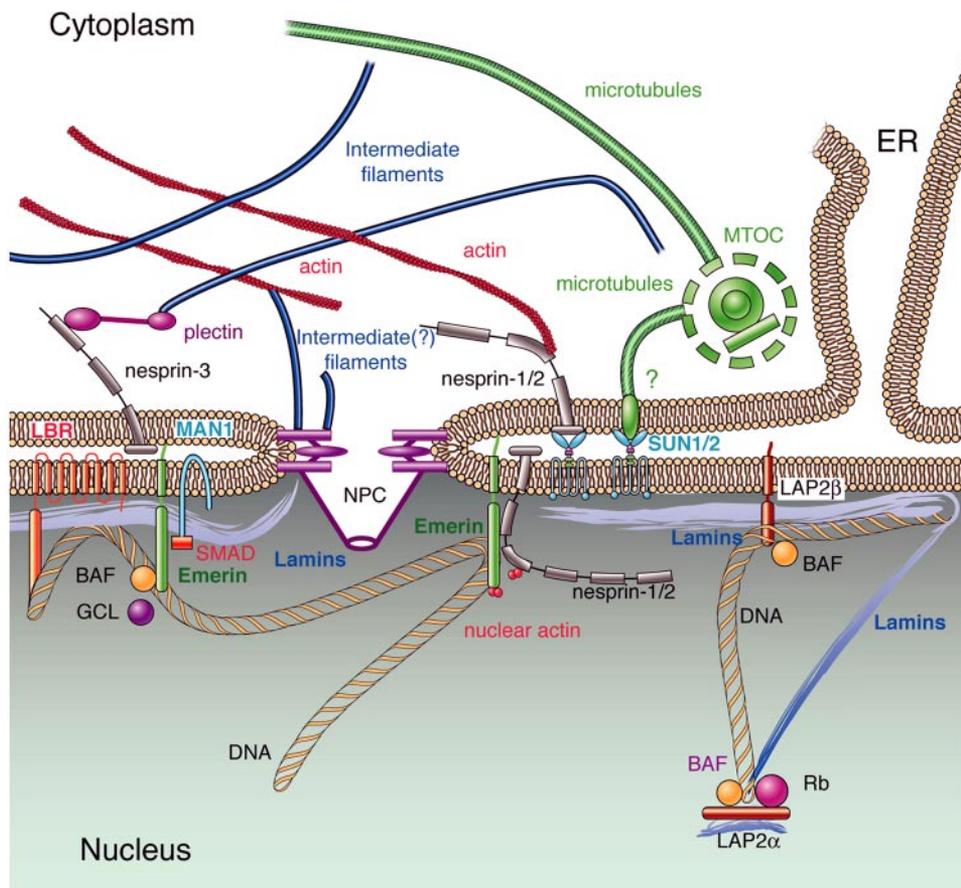


FIG. 5. Model of the location of nuclear lamins and their interaction with nearby localized proteins. Lamins bind directly to lamina-associated proteins (LBR, LAP2, emerin, MAN1, nesprins-1 and -2), but also to BAF, Rb, SREBP1, histone proteins, and DNA, and thereby mediate association with a scala of interacting structural proteins, including SUN1, actin, and possibly tubulin and intermediate filament proteins. Question marks indicate suggested but not yet proven interactions.

Knockdown of Ce-lamin causes nuclear morphological and mitotic defects (226), which might now be understood by considering downstream loss of function of other proteins. Knockdown of Ce-lamin leads to mislocalization of Ce-emerin and Ce-MAN1 to the ER. One other protein that no longer localizes to the NE following knockdown of Ce-lamin is Ce-BAF. Interestingly, RNAi knockdown of Ce-MAN and Ce-emerin also leads to failure of BAF to localize to the NE. RNAi knockdown of Ce-lamin, Ce-MAN1/emerin, or Ce-BAF all give rise to identical lethal mitotic phenotypes including the formation of anaphase chromatin bridges and aneuploidy (226, 228, 422). These findings imply that Ce-lamin is the central component of a complex including Ce-MAN1, Ce-emerin, and Ce-BAF that is essential for correct segregation of chromatin during mitosis.

The beauty of *C. elegans* is its simplicity. In general, because mammalian cells express many more lamins and NETs, there are important differences in the way protein complexes are assembled at the NE by lamins. However, it is now emerging that while the fine details may vary, the fundamental lessons learned from *C. elegans* are correct, and also apply to higher organisms.

In vertebrates, lamin associations with NETs have been investigated using cells obtained from knockout mice, by RNAi knockdown or through the use of domi-

nant negative mutants that disrupt lamin filaments. With the use of these approaches, it is evident that there are distinct A-type lamin-NET complexes and B-type lamin-NET complexes, although there may be overlap between the two (see Fig. 5). A-type lamins have been shown to bind to emerin in vitro, and the emerin binding site has been mapped to tail domain sequences common to lamin A and lamin C (61, 319). Similarly, the lamin A/C binding site in emerin has been mapped to sequences in the middle of its nucleoplasmic domain (215). In the absence of lamins A/C or after removal of lamins A/C from the lamina to nucleoplasmic aggregates in the presence of dominant negative lamin mutants, emerin is mislocalized to the ER (271, 360, 381). Importantly, absence of A-type lamins from the lamina does not lead to mislocalization of LAP2 β to the ER (381), suggesting that emerin and LAP2 β are anchored at the INM through different lamin complexes. This suggestion is supported by the finding that LAP2 β binds to B-type lamins in vitro (120) and a dominant mutant of lamin B₁ that disrupts lamin B filaments does lead to mislocalization of LAP2 β (324). Interestingly, the lamin A-emerin complex may also contain MAN1, since MAN1 is able to interact directly with emerin in vitro (242).

While emerin and LAP2 β appear to exist in distinct lamin complexes, both proteins bind to BAF through their

LEM domains (117, 215, 337), as does MAN1 (242). BAF is enriched at the INM in mammalian cells, although FRET and FLIP investigations suggest that it is relatively mobile at this site. Importantly, FRET analyses have revealed that BAF interacts directly with emerin at the INM (335). Expression of missense mutations of BAF in human cells inhibits assembly of emerin, LAP2 β , and lamin A into reforming nuclei. Consistent with this finding, emerin proteins containing mutations within the LEM domain are not recruited to the NE after mitosis (152). Similarly, peptides containing the LEM domain of LAP2 β inhibit lamina assembly (121). Therefore, as in *C. elegans*, BAF complexes appear to have important structural roles in mammalian cells. However, in mammalian cells it appears that two different BAF containing complexes might exist at the INM, one containing emerin and MAN1 that is tethered to A-type lamins, and a second containing LAP2 β that is tethered to B-type lamins.

B. Lamin Function in NPC Organization

A second important phenotype associated with RNAi knockdown of Ce-lamin is the clustering of NPCs within the ER (226). This phenotype is identical to a P-element disruption of lamin D_{m0} in *Drosophila melanogaster* (219) and implies that lamins or the nuclear lamina anchor NPCs within the NE and maintain their normal distributions. In *Xenopus* sperm, pronuclei B-type lamins interact with the COOH-terminal domain of nucleoporin Nup153 (345). Nup153 is located within the so-called nucleoplasmic ring of NPCs where it would be able to interact with lamin filaments (392). Moreover, disruption of lamin filaments with dominant negative lamin mutants causes a selective loss of Nup153 (but not other nucleoporins) from NPCs, suggesting the lamin filaments are needed to maintain Nup153 within the nucleoplasmic ring (345). Elimination of Nup153 does not prevent lamina filament assembly, but does lead to migration and clustering of NPCs within the NE (392). On the basis of these findings, it has been proposed that the nuclear lamina interact with the nucleoplasmic ring of NPCs via Nup153, thereby anchoring NPCs within the NE (175). Recently, another NPC protein, Nup53, has been shown to bind directly to lamin B, and anchors an NPC subcomplex containing Nup93, Nup155, and Nup205 within the NE (157).

C. Lamin and NET Function in Cytoskeleton Organization

C. elegans has also been exploited to investigate the role of lamin complexes in cytoskeleton organization. Three SUN domain proteins (sad1/UNC-84 homology), termed UNC-83, UNC-84, and matefin/SUN1, are located at the INM and ONM in *C. elegans* (216, 236, 237, 350).

Both UNC-84 and matefin/SUN1 are putative lamin binding proteins whose INM localization is dependent on Ce-lamin (although this has only been demonstrated directly for UNC-84). UNC-83 has been proposed to localize to the ONM by binding to UNC-84 in the lumen space of the nuclear membrane (147). Two additional proteins are also anchored to the ONM by matefin/SUN1 or UNC-84. ZYG-12 is a microtubule binding protein, belonging to the Hook family (391) which is anchored at the ONM by matefin/SUN1, where it tethers the centrosome to the NE (237). ANC-1 is the *C. elegans* homolog of nesprin-1 and is anchored to the ONM by UNC-84, where it interacts with the actin cytoskeleton (349). Therefore, by tethering UNC-84 to the INM, Ce-lamin maintains two independent protein complexes at the ONM, which interconnects the NE with either microtubules and the MTOC, or actin. Elimination of the Ce-lamin, UNC-84/matefin, ZYG-12 complex leads to disruption of centrosome migration on the one hand, which is manifest by a mitotic failure phenotype (237). Elimination of Ce-lamin, UNC-84, ANC-1 complexes leads to loss of contact with the actin cytoskeleton, which is manifest by a failure of nuclear positioning and migration (349).

It is now emerging that also in mammalian cells lamins anchor protein complexes to the NE that interact with the cytoskeleton.

1. Lamins bind to actin

The discovery of the nesprin family of cytoskeletal linker proteins has provided new impetus for understanding how elements of the cytoskeleton interact with the lamina (Figs. 5 and 6). Due to their independent discovery by three different groups, nesprins appear in the literature, variously as the nesprin-1 and -2 families, NUANCE, ENAPTIN, and syne 1 and syne 2 (5, 292, 420, 421). It is now generally agreed that nesprin will be the agreed nomenclature, with nesprin-1 corresponding to ENAPTIN and syne 1 and nesprin-2 corresponding to NUANCE and syne 2 (394).

Nesprin-1 binds to both lamin A and emerin in vitro, and it also self-associates (260). Nesprin-1 has also been shown to act as an actin bundling protein in vivo and in vitro (292). The actin bundling function of nesprin-1 implies an ONM localization (292). This is also consistent with one proposed function of nesprin-1 in anchoring of nuclei to postsynaptic membranes at neuromuscular junctions (5). However, because it binds directly to lamin A and emerin, nesprin-1 could also be located at the INM. Moreover, an INM localization might be consistent with the recent finding that nesprin-1 is involved in the anchorage of muscle A-kinase anchoring protein (mAKAP) to the NE in cardiomyocytes (296).

Nesprin-2 has also been shown to bind to A-type lamins and emerin in vitro, and its NE localization is

Cytoskeleton/nucleoskeleton interactions

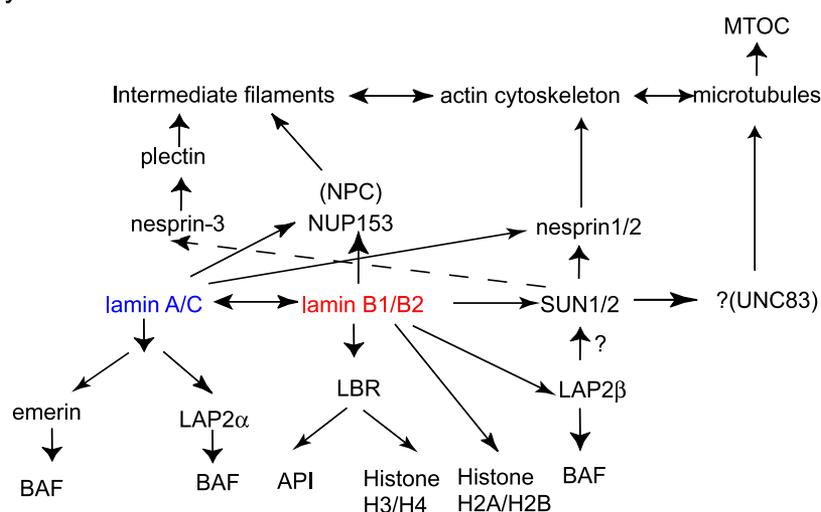


FIG. 6. Cytoskeletal/nucleoskeleton interactions. There is growing evidence that lamins play a central role in not only nuclear but total cellular cytoskeletal organization. Lamins bind to the nuclear pore complex, emerin, nesprins, and SUN1, which connects them to intermediate filament proteins, microtubuli, and actin. Probably several unknown proteins mediate these connections.

dependent on expression of lamin A or C (220, 419). The presence of nesprin-2 within lamin A/C complexes appears to be necessary for the localization of emerin to the INM, since dominant mutants of nesprin-2 can cause the mislocalization of emerin to the ER (220). However, nesprins-1 and -2 might also be anchored to the NE within complexes that do not involve A-type lamins. Both proteins interact with mammalian homologs of SUN1 through conserved COOH-terminal residues. Moreover, small interfering (si)RNA knockdown of SUN1 or expression of dominant negative SUN1 mutants both lead to mislocalization of nesprin-2 to the ER. Localization of SUN1 to the INM is not dependent on A-type lamins, implying the existence of distinct lamin-nesprin and SUN1-nesprin complexes (293). The existence of nesprin-Sun complexes has recently been confirmed by research showing that SUN2 is also involved in the formation of transnuclear membrane complexes (67). While extensive work on nuclear migration and/or centrosome localization has yet to be performed, the different protein complexes that exhibit these functions in *C. elegans* all appear to be present in mammalian cells.

Recent reports have shown an intriguing interaction between emerin and both α - and β -actin (211). In a complementary study, actin was also identified as a novel emerin binding protein together with alpha II spectrin using a proteomic approach. The same study revealed that emerin binds to and stabilizes the pointed ends of F-actin, thereby increasing filament assembly by >10-fold in vitro (167). These findings have led to the suggestion that emerin mediates the assembly of a cortical actin cytoskeleton at the NE (243, 399). Although cortical actin filaments have been described inside the NE of frog oocyte GV (243, 399), there is as yet no direct evidence for such filaments at the INM of somatic cells.

2. Lamins bind to microtubules

While in *C. elegans* binding of lamins to microtubules and the MTOC seems to be mediated by UNC-84 and UNC-83 (350; see also above), a direct physical connection of lamins to microtubules in mammalian cells is to be established. In *Drosophila*, such a connection of lamins via Klarsicht to the microtubules was demonstrated (299). Cells expressing a mutant lamin Dm₀ show loss of this connection, since normal nuclear migration in the *Drosophila* eye disk is lost, with the MTOC detaching from the nucleus in these cells (299). In mammalian cells, a connection of lamins to microtubules via SUN1 and an as yet unidentified ONM protein is anticipated (147).

3. Lamins bind to intermediate filaments

(Cryo)electron microscopy studies show a direct connection between the NPC and cytoplasmic filaments (199), which are presumably intermediate filaments (355). In addition, biochemical studies as well as cellular stretching experiments suggest a physical connection of cytoplasmic intermediate filament proteins to lamins via the NPC (see, e.g., Refs. 21, 370). Binding of desmin to the NPC appears to mediate the binding of the sarcomere to chromatin via lamins, and when cardiac myocytes are stretched, changes in the spatial arrangement of both the desmin-lamin intermediate filament network and the NE-associated chromatin can be observed. Stretch-induced changes in the chromatin, mediated by the intermediate filament-lamin connection, could be a mechanism to activate hypertrophy-associated genes (21). Additional proof for the lamin-desmin connection came from studies on *Lmna*^{-/-} cardiac cells showing a disorganized sarcomere and absence of desmin at the NPC complexes (282). Also other members of the intermediate filament

protein family seem to be affected by the absence of A-type lamins. *Lmna*^{-/-} fibroblasts show a disorganization of the vimentin network (38). In addition to the suggested connection of intermediate filaments with NPC proteins, a very recent study showed that cytoplasmic intermediate filaments bind to the ONM protein nesprin-3 via plectin proteins (398). Whether nesprin-3 is also connected to nuclear lamins via molecules such as SUN1 remains to be examined.

V. THE NUCLEAR LAMINA DURING APOPTOSIS

Studies on the behavior of lamins during the process of programmed cell death (apoptosis) have not only stressed the importance of lamins in the execution phase of cellular and especially nuclear degradation during apoptosis, but have also yielded new insights into the molecular organization of the nuclear lamina and the nuclear membrane.

Although it has been shown that lamins are substrates for caspases, little is known about the steps that govern the proteolysis of the higher order structures of the nuclear lamina during apoptosis. Lamina degradation is likely to be an important step in terminating cell function by degrading the structural support of a cell's nucleus, since in cells transfected with lamins containing a mutated caspase cleavage site nuclear degradation during apoptosis was largely delayed (312). Caspase-6 has been identified as the major protease responsible for lamin A degradation (343), while Lee et al. (217) showed that lamin A cleavage and apoptosis could be entirely abrogated by peptide inhibitors of caspase-6. The A-type lamins are cleaved at their conserved VEID site, which is located in the nonhelical linker region L12 at position 227–230. This region contains chromatin-binding sites (135) and is also involved in the formation of the lamina structure (251). It has been assumed that caspase-6 is also responsible for B-type lamin cleavage at their conserved VEVD site at position 227–230. However, studies using cell-free extracts immunodepleted of either caspase-3 or -6 showed that proteolysis of lamin B was unaffected by the removal of caspase-6, which suggests that lamin B degradation during the execution phase of apoptosis could also be achieved through caspase-3 activity (343). Only recently Lavastre et al. (212) demonstrated that lamin B1 degradation could be reversed by a caspase-6 inhibitor, but not by a caspase-8 inhibitor.

Several years ago we performed a comprehensive study on the dynamics and the consequences of lamin cleavage during apoptosis in living cells, to obtain a better understanding of the rapid and coordinated breakdown of the complex structure of the nucleus (34). Induction of apoptosis in A-type lamin-GFP transfected cells revealed a loss of the GFP-tagged lamina structure at the periphery

of the nucleus, with a simultaneous translocation of the GFP to the nucleoplasm and cytoplasm of the cell. Very rapidly after A-type lamin relocalization (within a few minutes) chromatin condensation became visible. Immunoblotting of apoptotic cells revealed that only part of the A-type lamin proteins had been cleaved, while the majority of these proteins were apparently still intact but solubilized. Oberhammer et al. (287) already reported a small increase in soluble, depolymerized intact lamin monomers before the major onset of DNA condensation in apoptosis. In contrast to the A-type GFP-tagged lamins, no lamin B1-GFP signal was observed in the cytoplasm in early apoptotic cells. Furthermore, a lamina-like structure at the periphery of the nucleus could still be observed for lamin B1 in cells several hours after the onset of DNA condensation. FLIP studies in living cells supported this finding, since repetitive bleaching did not cause complete bleaching of lamin B1-GFP signal, while the lamin C-GFP signal was lost. The observation that lamin B1 fragments remain visible as a nuclear structure during apoptosis is in accordance with findings of Buendia et al. (44), who showed that during apoptosis the majority of the proteolytic fragments of lamin B2 remain associated with an insoluble structure, whereas the majority of the proteolytic fragments of Nup153, a component of the NPCs, is released into the cytoplasmic compartment.

It can be speculated that the differences in translocation behavior between A- and B-type lamins during the apoptotic cascade reflect differences in molecular organization between the lamin subtypes at three different levels.

1) A- and B-type lamins differ in the processing of their COOH terminus. As mentioned above, mature B-type lamins retain their hydrophobic isoprene tail, whereas the A-type lamins lack this anchoring site for the nuclear membrane. It has previously been reported that the CaaX motif in this tail domain is necessary for the efficient integration of lamin B into an already formed lamina, since lamin B CaaX⁻ mutants showed reduced targeting to the lamina, and appeared not to be associated with membranes at mitosis. This indicates that the modifications at the CaaX motif are responsible for the association of lamin B with the nuclear membrane (258). It has been previously shown that nuclear membranes still surround chromatin fragments formed during apoptosis (194, 213, 286). Apparently the lateral or head-to-tail assembly of lamin B1 molecules (359) is sufficient to ensure that both the NH₂-terminal and COOH-terminal fragments of lamin B1 remain attached to this nuclear membrane, even after apoptotic lamin cleavage.

2) A- and B-type lamins interact with different lamina-associated proteins, which could cause differences in translocation during apoptosis. The COOH terminus of LAP2 α binds directly to residues 319–566 in A-type lamins, which include the COOH terminus of the rod and

the entire tail (120). During apoptosis, when LAP2 α is cleaved in a caspase-dependent manner, the apoptotic COOH-terminal fragment of LAP2 α remains associated with a residual framework upon extraction using detergent/salt buffers, whereas the NH₂-terminal fragment is extracted from intranuclear structures (141). LAP2 β binds specifically to a region within coil 1B of B-type lamins (120) and to chromatin, but has low affinities for A-type lamins (108, 176). In contrast to LAP2 α , LAP2 β is integrated into the inner nuclear membrane by its COOH-terminal domain. It has been reported that LAP2 β is cleaved during apoptosis, probably by the activity of caspase-3 (44). Furthermore, it was shown that cleavage of both LAP2 β and lamin B2 started at about the same time point in the apoptotic process.

LBR is an integral protein of the inner nuclear membrane that interacts with B-type lamins, but not with A-type lamins (see however Ref. 258). It has been reported that the NH₂-terminal domain of LBR is specifically cleaved at a late stage of apoptosis, subsequent to the cleavage of lamin B (88). Another study failed to observe any apoptotic cleavage products of LBR even after long periods of apoptosis induction, whereas lamin B2 had already been cleaved (44).

Interactions between LAP2 β and LBR, which are cleaved at late stages of apoptosis, with the relatively early-cleaved lamin B1 can cause these fragments to impart structural support to the nuclear membrane, a property that might be important in the formation of apoptotic bodies.

3) It has been reported that efficient lamina disassembly during apoptosis requires both lamin hyperphosphorylation by PKC- δ and caspase-mediated proteolysis (32, 70). However, if phosphorylation is important for lamina disintegration during apoptosis, one would not expect solubilization of lamins in the presence of staurosporine, a well-known kinase inhibitor, which can be used to induce apoptosis (34). However, Park and Baines (297) recently showed that herpes simplex virus (HSV)-1 infection induced the phosphorylation of both lamin B and PKC and that elevated lamin B phosphorylation in HSV-1-infected cells was partially reduced by inhibitors of PKC. Their data suggest a model in which kinases that normally disassemble the nuclear lamina during apoptosis are recruited to the nuclear membrane and that in particular the recruitment of PKC functions to phosphorylate lamin B to help modify the nuclear lamina.

VI. LAMIN AND NUCLEAR ENVELOPE TRANSMEMBRANE PROTEIN FUNCTION IN DNA REPLICATION AND TRANSCRIPTION

Both lamins and NETs have reported functions in DNA replication and transcription. However, it is impor-

tant to note that, due to the complex nature of these processes, their exact role is still rather elusive. Functional studies are in general performed in artificial models involving large-scale disruption of lamin molecules, the lamina or the complete nuclear membrane. As a result, changes in cellular functioning, ascribed to lamin modifications, could be secondary effects resulting from the particular treatment. Indeed, several conflicting papers on the functions of lamins have been published (see below). Some suggested functions in transcription occur at the INM and involve the formation of repressor complexes. Other functions appear to occur within the nucleoplasm and imply that lamins, particularly A-type lamins, are localized in nuclear bodies, where they must interact with binding partners that are not integral membrane proteins. Recently, it has emerged that A-type lamins have important roles in regulating adult stem cell differentiation and that these roles fail when lamin A is mutated. Therefore, understanding how lamins function in transcription regulation is probably crucial for understanding the pathophysiology of at least some of the lamins A/C-related diseases.

A. Role of B-Type Lamins in DNA Replication

The first reports that lamin were involved in DNA replication arose from studies using cell-free extracts of *Xenopus* eggs that support the assembly of replication-competent nuclei in vitro. Physical or functional depletion of endogenous B-type lamins from these extracts, using antibodies, resulted in assembly of nuclei that had a fragile NE and functional NPCs, but which lacked a lamina and were unable to replicate DNA (185, 253, 279). Lamin B₁ has also been reported to localize to centers of DNA replication during S phase in cultured cells (263, 304). Therefore, it appeared that B-type lamins might have a direct role in DNA synthesis. The mechanism by which lamins influence DNA replication is, however, contentious. Dominant negative lamin mutants, lacking tail domain sequences, have been used to either inhibit lamina assembly or to disrupt the lamina of fully assembled and replicating nuclei. Using this approach, one group has reported that B-type lamins accumulate as nucleoplasmic aggregates that recruit proteins involved in the elongation phase of DNA replication, leading to the suggestion that lamins are involved in the elongation phase of DNA replication (264, 348). In contrast, two other groups have reported that preventing lamina assembly inhibits the initiation phase of DNA replication, whereas disruption of the lamina in nuclei that have already initiated DNA replication does not inhibit run-on synthesis, implying that lamins are required for the initiation but not the elongation phase of DNA replication (92, 179). Furthermore, these studies show that recruitment of proteins involved

in the elongation phase of DNA replication to nucleoplasmic lamin aggregates is artifactual and does not interfere with preassembled replication complexes (179). Moreover, a complex of LAP2 β and HA95 has also been shown to be required for the initiation but not elongation phase of DNA replication. Apparently, this complex prevents targeting of the initiation protein cdc6 for destruction by the proteasome (249). Therefore, one explanation for the role of B-type lamins in the initiation of DNA replication is that they recruit the LAP2 β /HA95 complex to the INM, thereby stabilizing cdc6.

B. Role of Lamins in Transcription

Both A-type and B-type lamins have reported functions in transcription regulation. In both embryonic and somatic cells, B-type lamins can bind to RNA polymerase II, and disruption of the lamina using dominant negative mutants inhibits polymerase II activity (347). This finding implies that B-type lamins are involved in the basic process of RNA synthesis. In contrast, A-type lamins appear to influence the activity of proteins that regulate transcription. A-type lamins have been reported to bind to four different transcription regulators, namely, the Kruppel-like protein MOK2 (87), the sterol response element-binding protein SREBP1 (229), the pocket protein retinoblastoma protein (Rb) (291), and direct interaction with c-Fos (178). While it has yet to be established that A-type lamins can influence either MOK2 or SREBP1 activity, a role for A-type lamins in regulating Rb function is now well established.

Rb functions by repressing the activity of the E2F-DP3 transcription factor complex, which is required for activation of expression of genes required for entry into S phase of the cell cycle (204). It has been shown that Rb function as a transcriptional repressor is correlated with it being tethered to structures in the nucleus and that oncogenic deletions in its COOH terminus prevent its nuclear tethering (261). Tethered Rb has been localized to nucleoskeleton filaments that have the dimensions of intermediate-like filaments (238). Two lines of evidence suggest that these filaments contain A-type lamins. First, A-type lamins form a salt-resistant complex together with LAP2 α within the nucleoskeleton (77). Second, this complex tethers Rb within the nucleus of cells in G₁ phase of the cell cycle, through its pocket C domain (246). Tethering of Rb in the nucleus is apparently a protective mechanism. In fibroblasts from a *Lmna* $-/-$ mouse, Rb is targeted for destruction by the proteasome, and as a result, the fibroblasts display growth characteristics that are indistinguishable from fibroblasts from an *Rb* $-/-$ mouse (186). Whether Rb is destroyed in the nucleus or in the cytoplasm is as yet unknown (Fig. 7). Recently, a direct interaction of lamins A/C with c-Fos has been dis-

covered. Interaction of A-type lamins with c-Fos resulted in suppression of AP-1 and a decrease in proliferation in mouse embryonic fibroblasts. Conversely, cells lacking A-type lamins showed increased proliferation rates (178).

C. Role of NETs in Transcription Regulation and Signal Transduction

There is growing evidence the NETs also regulate transcriptional and signal transduction pathways. Some of this evidence is circumstantial and is based on associations between particular NETs and transcriptional regulators or silencing proteins, and as yet functional data are lacking. For example, LBR binds to a number of chromatin-associated proteins that are involved in higher order chromatin organization. These include histone H3-H4 tetramers, the chromatin-associated protein HA95, and the chromodomain protein HP1 (307, 411, 412). The binding of LBR to these proteins is correlated with a lamin-dependent association of heterochromatin to the NE (282, 360). Similarly, the ubiquitous transcription factor germ-cell-less (GCL) (188) exists in a trimeric complex with emerin and lamin A and competes with BAF for emerin binding sites (168). The GCL/BAF binding site in emerin is also recognized by a death-promoting repressor Btf, although Btf binding to emerin may be independent of GCL/BAF (150).

For two NETs, there is direct evidence that they influence transcription and cell signaling pathways. GCL is able to inhibit the DP3 subunit of the E2F-DP3 complex independently of Rb (79). It has now been

Interactions of lamins with transcription factors

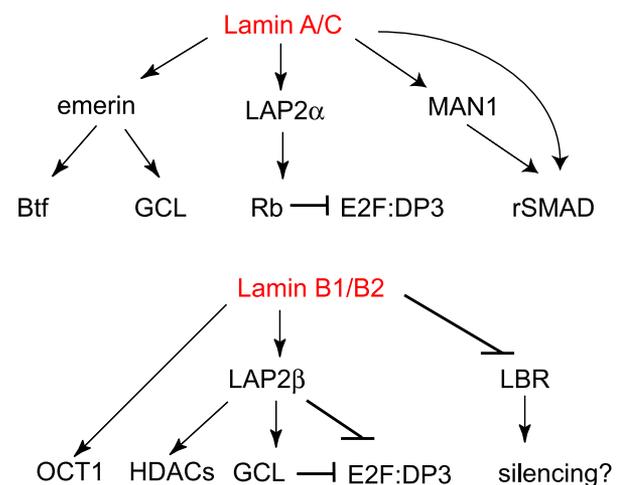


FIG. 7. Interactions of lamins with transcription factors. Although lamins themselves do not act as transcription factors, there is growing evidence that their interaction with several transcription regulatory proteins can explain the occurrence of a variety of lamin-associated diseases.

shown that LAP2 β binds to GCL at the INM and either together with GCL or on its own can repress E2F-DP3 activity (283). Interestingly, LAP2 β /GCL-mediated repression of E2F-DP3 is as strong as Rb-mediated repression. Therefore, the LAP2 β /GCL may provide an Rb-independent mechanism for controlling cell proliferation or differentiation (147).

Recently, it has been shown that MAN1 binds to the receptor regulated SMAD (rSMAD) through its COOH-terminal domain (222, 289). rSMADs are activated by members of the transforming growth factor (TGF)- β superfamily of growth factors, particularly the bone morphogenic proteins (BMPs) (366). After activation, rSMADs accumulate in the nucleus as multimeric complexes where they regulate the expression of multiple genes. In developing *X. laevis* embryos, maternally expressed MAN1 is restricted to ectoderm at the gastrula stage of development and to neuroectoderm at the neurula stage. When MAN1 is expressed ventrally, it induces a partial secondary axis, by antagonizing BMP signaling, implying that MAN1 might inhibit rSMAD function (289). It has now been established that MAN1 interacts with rSMADs at the INM through the rSMAD RNA recognition motif. Overexpression of MAN1 inhibits rSMAD phosphorylation, dimerization with SMAD4, and nuclear translocation, and this in turn antagonizes TGF- β signaling. Importantly, overexpression of a MAN1 mutant that is unable to bind rSMAD has no influence of TGF- β signaling (294). It has now been reported that lamin C may also influence rSMAD phosphorylation and function. In fibroblasts from a *Lmna* $-/-$ mouse, rSMAD is hyperphosphorylated, compared with wild-type fibroblasts, 24 h after TGF- β stimulation, and this hyperphosphorylation is correlated with overexpression of collagen. Both rSMAD hyperphosphorylation and collagen overexpression are rescued by transfection of *Lmna* $-/-$ fibroblasts with lamin C (374). Whether MAN1 and lamin C act through the same pathway or through divergent pathways is as yet unclear, particularly as lamin C is not expressed in early embryos.

VII. LAMINOPATHIES AND NUCLEAR ENVELOPATHIES

Nuclear envelopathies are the group of diseases caused by mutations in genes encoding nuclear envelope proteins. Disease-causing mutations are currently reported for seven genes, i.e., *EMD*, *LMNA*, *FACE-1* (or *ZMPSTE24*), *LBR*, *MAN1*, *LAP2*, and *AAAS* (Fig. 8). This section is mainly devoted to the major class, laminopathies, caused either by mutations in the lamin A/C (*LMNA*) gene (i.e., primary laminopathies) or by mutations in the *FACE-1* gene affecting the correct posttranslational processing of prelamin A, and thus now considered as secondary laminopathies. Primary laminopathies

fall into five classes affecting either specific tissue in isolated fashion, i.e., 1) the striated muscles, 2) the peripheral nerves, and 3) the adipose tissue; or in a systemic way several tissues with 4) the premature ageing syndromes and their related disorders, named also "systemic laminopathies." Finally, numerous heterogeneous clinical situations have been reported and form a fifth group of disorders that comprise overlapping phenotypes characterized by the coexistence of two or more tissue involvements.

Until now, more than 211 different mutations have been identified in the *LMNA* gene in 1,037 individuals presenting one of these different types of laminopathies (Fig. 9, for details see UMD-*LMNA* database at www.umd.be: 2000). Relations between phenotypes and genotypes are far from being clear. Indeed, there is no relation between the phenotype, the type, and/or the localization of the mutation for striated muscle laminopathies, as *LMNA* mutations leading to this type of laminopathies are spread all along the gene. In contrast, the majority of laminopathies affecting specifically the adipose tissue are due to mutation affecting codon R482. Similarly, some other laminopathies are due to only specific *LMNA* mutations, i.e., peripheral nerve laminopathies and two premature ageing syndromes, the mandibuloacral dysplasia and the Hutchinson-Gilford progeria.

With regard to other nuclear envelope-related diseases, it can be stated that, with the exception of the X-linked form of Emery-Dreifuss muscular dystrophy due to *EMD* mutations (up to 238 patients) carrying one of the 93 different *EMD* mutations reported so far (for details see below and UMD-*EMD* database at www.umd.be: 2010), the clinical and genetic aspects of the *LBR*, *LAP-2*, *MAN1*, and *AAAS* gene-related disorders are only in the first steps of their descriptions.

While mouse models for different diseases start to emerge, it is important to note that clinical symptoms, present in humans, can be absent from diseased mice with a comparable genotype. Moreover, characteristic features of diseased human cells can be reversed in mouse models. For instance, fibroblasts from a patient lacking A-type lamin expression show reduced proliferative capacity (271), while similar cells from *Lmna* $-/-$ mice show increased proliferation rates (178, 374). Therefore, great caution is needed with interpolating mice findings to the human situation.

A. Striated Muscle Laminopathies

The pure striated muscle involvements account for ~60–70% of the currently known lamins A/C-related disorders (see UMD-*LMNA* database at www.umd.be:2000).

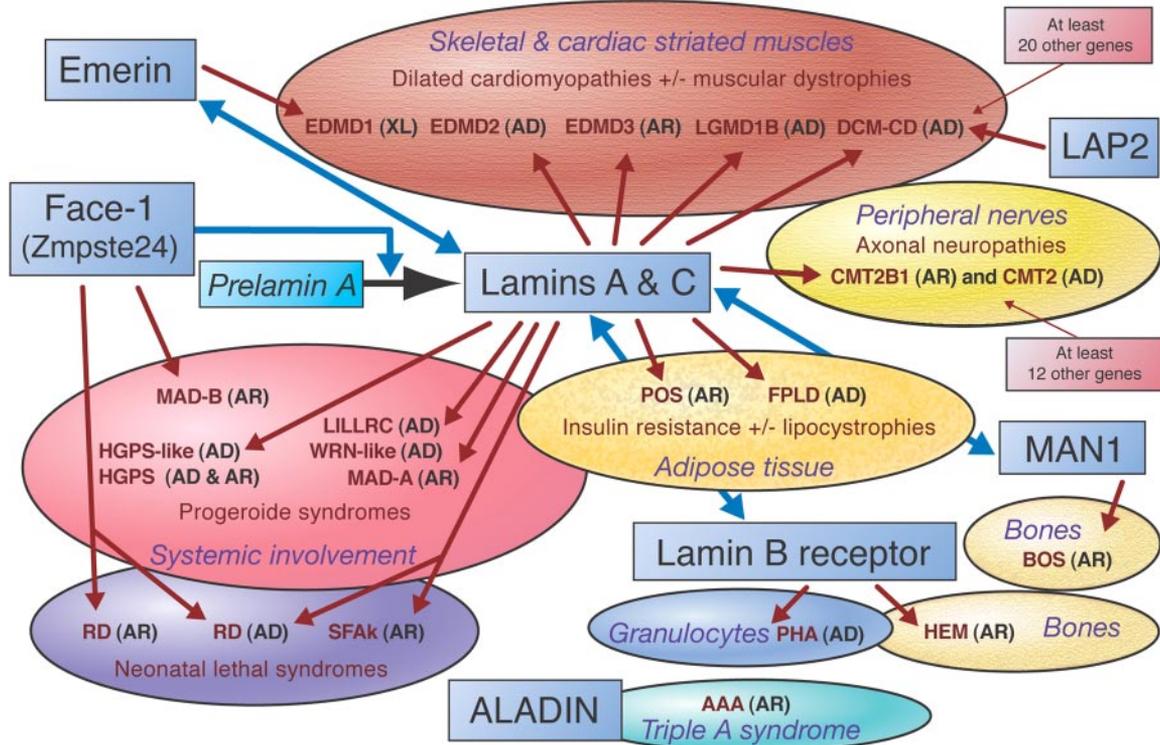


FIG. 8. Nuclear envelopathies: schematic representation of current spectrum of nuclear envelopathies. OMIM acronyms are used to indicate the names of the different disorders. AR (autosomal recessive) and AD (autosomal dominant) designate the mode of inheritance of the diseases.

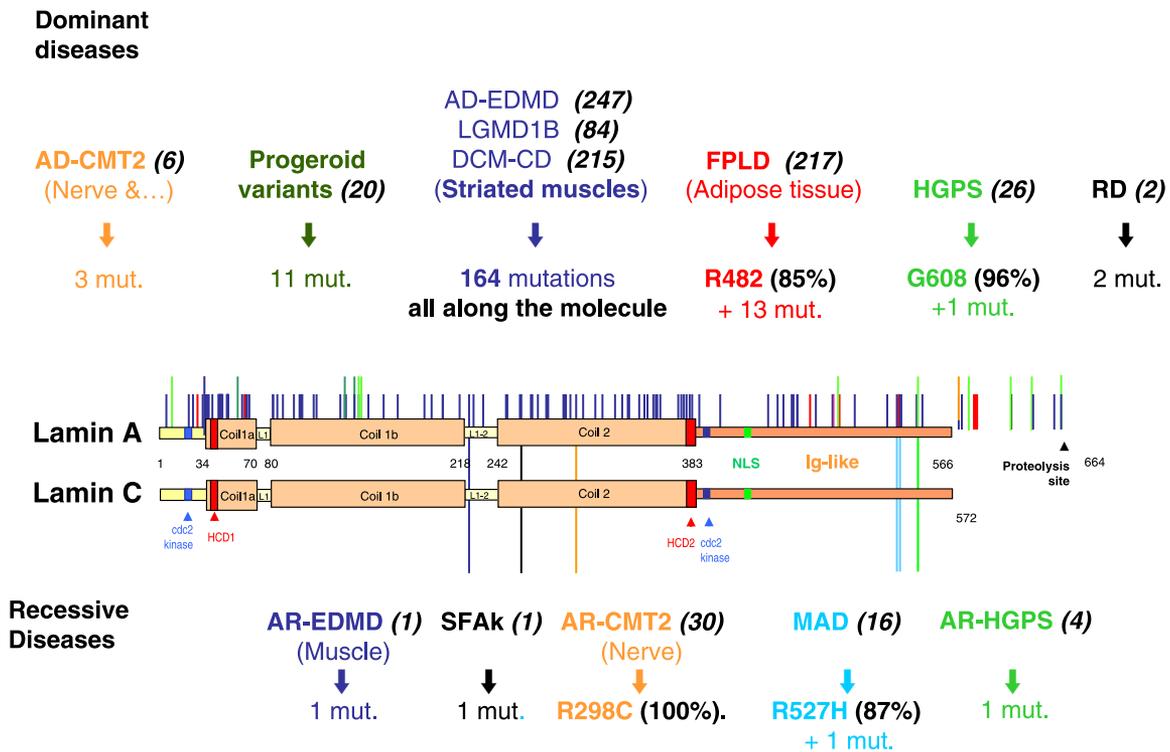


FIG. 9. Spectrum of LMNA mutations: schematic representation of LMNA mutations identified in the various types of laminopathies. Dominant disorders due to heterozygous LMNA mutations are depicted on the top of the protein scheme, whereas recessive disorders due to homozygous mutations are presented below. Up to now, a total of 211 different LMNA mutations were identified in 1,037 individuals (for more details, see UMD-LMNA mutation database at www.umd.be). Numbers in parentheses in black close to each disease acronym indicate the numbers of individuals carrying a LMNA mutation and presenting the corresponding phenotype.

1. Emery-Dreifuss muscular dystrophy

Emery-Dreifuss muscular dystrophy (EDMD) is a rare skeletal muscle and cardiac condition characterized by the clinical triad of early joint contractures involving elbows, Achilles tendons, and postcervical muscles, slowly progressive muscle weakness and wasting initially in a humeroperoneal distribution, and cardiac involvement frequently associating conduction defects, arrhythmias, and dilated cardiomyopathy, which is the most serious and life-threatening clinical manifestation of the disease. EDMD is inherited in an X-linked (XL-EDMD), autosomal dominant (AD-EDMD) or autosomal recessive (AR-EDMD) trait (162) and is related to mutations in two genes, *EMD* encoding emerin (19) for XL-EDMD and *LMNA* encoding lamins A and C (23, 310) for the autosomal forms. The XL-EDMD had similar neuromuscular and cardiac involvement as the autosomal EDMD. Their main clinical characteristic features have been described in a large series of EDMD patients carrying *EMD* or *LMNA* mutations (9, 25, 27, 42, 102, 240, 310, 390, 404, 410). EDMD diagnosis may not be based on nonmolecular testing currently applied to muscular dystrophies, since most of them bring nonspecific findings in this disease. Creatine kinase levels are normal or moderately elevated and decrease with age (16, 22, 25), and electromyographic testing usually shows myopathic features with normal nerve conduction studies. Muscle biopsy shows nonspecific myopathic or dystrophic changes, while electron microscopy can reveal specifically alterations in nuclear architecture (103, 104, 318, 331). Muscle imaging shows a diffuse pattern of muscle CT-scan involvement affecting biceps, soleus, peroneal, external vasti, gluteus, and paravertebral muscles (144). A characteristic involvement of posterior calve muscles on MRI has been reported in AD-EDMD forms (Fig. 10, A and B) (254).

A) THE X-LINKED FORM OF EDMD (XL-EDMD). The first cases were described by Dreifuss and Hogan (86) and Emery and Dreifuss (96) in a Virginian kindred in which there were eight affected males in three generations. Female carriers can exhibit isolated cardiac defects (94) in the absence of any skeletal muscle abnormality. Since then, several families were reported with similar features and X-linked transmission (156, 170, 256, 316, 330, 368, 388). XL-EDMD gene is inherited as a recessive character, with 100% penetrance by the second/third decade of life. Heterozygous females are usually asymptomatic. However, some females rarely exhibit either cardiac involvement with arrhythmia and bradycardia and risk of sudden death (17, 95, 105, 256, 305) or a complete EDMD phenotype, generally in relation with variable chromosome X inactivation in these females (47, 240). The first molecular defects in XL-EDMD were identified via positional cloning on chromosome Xq28 in the *STA* gene (now called *EMD*), encoding a new protein that was called emerin (19). Pro-



FIG. 10. Examples of patients suffering from three different laminopathies. A and B: EDMD with joint contractures (elbows, ankles) and diffuse muscle wasting of humeroperoneal predominance. C–F: LGMD1B without joint contractures but muscle wasting of pelvifemoral predominance. G and H: partial lipodystrophy of Dunnigan type with buffalo neck, absence of subcutaneous fat tissue, and muscle pseudohypertrophy in the lower limbs.

duction of specific antibodies against this new protein revealed that it was actually a ubiquitously expressed protein of the inner nuclear membrane (239, 275). Numerous mutations of all types (missense, nonsense, frame-shift insertions and deletion, splice sites) have been found in *EMD* (20, 201, 240, 281, 404, 410) (for a complete list of the *EMD* mutations, see UMD-*EMD* mutation database at www.umd.be:2010). The majority of *EMD* mutations are null mutations with the same consequence: a complete absence of emerin in all nuclei. They are spread all along the gene without hot-spot or recurrent mutations. Few missense mutations are correlated with decreased or normal amounts of emerin and result in a mild EDMD phenotype (93, 410).

B) THE AUTOSOMAL DOMINANT EDMD (AD-EDMD). During the 1970s and the 1980s, several authors reported families where the EDMD phenotype appeared to be transmitted as an autosomal trait (54, 259, 288, 317, 329, 400). This was confirmed soon after the identification of the emerin defect in the XL-EDMD. Indeed, it was evident that EDMD is genetically heterogeneous as several EDMD patients were not carrying *EMD* gene mutations (20). Hauptmann-Thannhauser eponym was sometimes suggested (11) to be attached to autosomal muscular dystrophy with early contractures and cardiomyopathy, as Hauptmann reported in 1941 (155).

With the use of genetic linkage analysis, the locus for AD-EDMD was mapped to an 8-cM interval on 1q11-q23 in a large French pedigree, and mutations were identified in the *LMNA* gene (23): one nonsense and three missense mutations. These results represented the first identification of mutations in a component of the nuclear lamina as a cause of an inherited muscle disorder. Since this first description, numerous other *LMNA* mutations were reported in AD-EDMD patients (25, 27, 42, 390; for a complete list, see UMD-*LMNA* mutation database at www.umd.be:2000). These mutations are mainly missense mutations, although nonsense mutations, small in-frame and out-of-frame deletion/insertions and splice site mutations also occur (26); they are spread all along the gene with no relation between the location or type of mutation and the severity of the phenotype (25, 255, 390).

In AD-EDMD form, emerin is normally expressed. Distribution of emerin was found to closely resemble that of lamins A and C (241). A functional interaction between emerin and lamin A in the nucleus could explain the identical phenotype in the different forms of EDMD.

Morphological and immunological analysis of skin fibroblasts from AD-EDMD patients carrying *LMNA* mutations revealed honeycomb nuclear structures and nuclear envelope blebs in patient cells (100, 270). Concentrated foci of lamin A/C in the nucleoplasm were also observed. In our experience, only mutations in the head and tail domains of lamins A and C significantly altered the nuclear architecture of patient fibroblasts. These re-

sults confirm that mutations in lamins A and C may lead to a weakening of a structural support network in the nuclear envelope in fibroblasts and that nuclear architecture changes depend on the location of the mutation in different domains of lamin A/C (270).

C) AUTOSOMAL RECESSIVE EDMD (AR-EDMD). The existence of AR-EDMD was suspected before the identification of the *LMNA* defect in AD-EDMD (362). Until now, only one homozygous *LMNA* gene mutation in a 40-yr-old man with severe EDMD was identified (310). His parents, who were first cousins, were asymptomatic and carriers of the *LMNA* heterozygous mutation. The patient had experienced difficulties when he started walking at age 14 mo. At age of 5 yr, he could not stand because of contractures. At the age of 40 yr, he presented with severe and diffuse muscle wasting and was confined to a wheelchair. Careful cardiological examination showed that he did not experience cardiac problems.

2. Dilated cardiomyopathy with conduction system defects (DCM-CD)

Dilated cardiomyopathy (DCM) is characterized by cardiac dilation and reduced systolic function, and represents an outcome of heterogeneous group of inherited and acquired disorders. Causes include myocarditis, coronary artery disease, systemic diseases, and myocardial toxins. Among patients with idiopathic DCM, in which these causes are excluded, familial occurrence accounts for up to 35% (173). Except for the cases resulting from mutations in dystrophin or in mitochondrial genes, the autosomal forms of DCM are the most frequent and can be further grouped into either a pure DCM phenotype, DCM with cardiac conduction system disease (DCM-CD), and DCM associated with other clinical features. Numerous loci for autosomal forms of DCM have been mapped, and up to 21 different genes were identified (for reviews, see Refs. 173, 192). Among the loci identified for DCM-CD, the locus *CMD1A* had been mapped on chromosome 1p1-q21, which overlaps with the region where the *LMNA* gene is localized (191). Analysis of families with autosomal dominant DCM-CD linked to the *CMD1A* locus, identified five heterozygous mutations: four affecting the α -helical rod domain of lamins A and C and one affecting the lamin C specific tail domain (99). Each mutation caused heritable, progressive conduction system disease (sinus bradycardia, atrioventricular conduction block, or atrial arrhythmias) and dilated cardiomyopathy. Heart failure and sudden death occurred frequently within these families. No family members with mutations had either joint contractures or skeletal muscle myopathy. Furthermore, serum creatine kinase levels were normal in family members with mutations in the lamin rod domain, but mildly elevated in some family members with a defect in the tail domain of lamin C (99). It is interesting to note that

several patients from the large French pedigree which allowed the identification of the AD-EDMD locus had isolated DCM-CD without skeletal muscle symptoms, further demonstrating that AD-EDMD and CMD1A are allelic disorders (9). Since then, numerous other *LMNA* mutations were reported in patients with isolated DCM-CD (6, 184, 190, 326, 363) (for a complete list, see UMD-*LMNA* mutation database at <http://www.umd.be>: 2000).

Very recently, it has been suggested that DCM can also be caused by a mutation in the *LAP2* gene, which causes an Arg690Cys substitution in the *LAP2* α isoform (364). This mutation causes a decreased interaction of this protein with A-type lamins.

3. Limb-girdle muscular dystrophy type IB (LGMD1B)

Limb-girdle muscular dystrophy (LGMD) constitutes a clinically and genetically heterogeneous group of muscular disorders characterized by proximal muscle weakness and wasting (Fig. 10, C–F). These disorders are inherited in a dominant (LGMD1) or recessive (LGMD2) manner. Among the autosomal dominant forms, LGMD1B was first described in three families in whom skeletal muscle involvement was associated with cardiac disease (376, 377). Rigid spine was absent, and elbow and Achilles tendon contractures were either minimal or late, and calf hypertrophy was occasionally present, distinguishing this disorder from EDMD. Cardiological abnormalities were found in these patients, including atrioventricular conduction disturbances and dysrhythmias, presenting as bradycardia; syncopal attacks needed pacemaker implantation. Also, sudden cardiac death is often observed. Positional cloning identified a locus on chromosome 1q11-q21 (377). In these three original LGMD1B families, *LMNA* mutations were identified demonstrating that LGMD1B and AD-EDMD are also allelic disorders (269). Shortly after this first description of *LMNA*, a mutation in LGMD1B, a large family was reported in which a same *LMNA* mutation was leading to either EDMD, DCM-DC, or LGMD1B phenotypes in the various affected family members (33), confirming further the allelic characters of AD-EDMD, CMD1A, and LGMD1B. Since then, other families showing LGMD1B phenotype with other *LMNA* mutations were identified (14, 195, 200, 271) and confirmed the clinical specific features of this condition.

As for AD-EDMD, we investigated the consequences of various *LMNA* mutations on nuclear architecture in skin fibroblasts from patients with LGMD1B or CMD1A. Regardless of the disease, we observed the same type of nuclear defects, i.e., honeycomb nuclear structures and nuclear envelope blebs, confirming a common pathogenic pathway of the *LMNA* mutations (270).

4. Other skeletal and cardiac conditions

In addition to these three main striated muscle laminopathies, other atypical presentations have been reported, highlighting the clinical variability of both skeletal and cardiac involvement and suggesting a continuum among this type of laminopathies.

A) QUADRICIPITAL MYOPATHY AND DILATED CARDIOMYOPATHY. This entity was reported in a large family (56). Cardiac involvement preceded neuromuscular disease in all affected patients, with an average age at onset of cardiac symptoms of 40 yr. A *LMNA* mutation (R377H) was found, identical to the mutation found in another family with LGMD1B (269), suggesting that the quadricipital myopathy with dilated cardiomyopathy is probably a minor expression of the LGMD1B.

B) DCM-CD INCLUDING APICAL LEFT VENTRICULAR ANEURYSM WITHOUT ATRIOVENTRICULAR BLOCK. A *LMNA* mutation (R541C) was found in two members of a French family with a history of ventricular rhythm disturbances and atypical form of dilated cardiomyopathy with left ventricle aneurysm revealed by ventricular rhythm disturbances without atrioventricular block (112).

Early atrial fibrillation is characterized by rapid and irregular activation of the atrium that may cause thromboembolism, tachycardia-mediated cardiomyopathy, heart failure, and ventricular arrhythmia. Screening of the *LMNA* gene in DNA samples from 66 cases of DCM with or without associated features identified a *LMNA* mutation in one family with early onset of atrial fibrillation (326).

Dropped head syndrome is characterized by severe weakness of neck extensor muscles with sparing of the flexors. It can be observed in several neuromuscular diseases, but it may also be an isolated feature with uncertain etiology. Recently, one child showing isolated dropped head syndrome was found to carry a *LMNA* mutation (74).

5. The cardiac disease of striated muscle laminopathies is life-threatening

The cardiac disease, a common feature of all these striated muscle laminopathies, is characterized by atrial fibrillation, conduction-system disturbances, sudden death, and heart failure (363, 373). The incidence of cardiac sudden death among carriers of *LMNA* mutations is extremely high (9, 27, 373). As most of these sudden cardiac death are mainly due to sustained ventricular tachyarrhythmias that cannot be prevented by the classical pacemaker devices, a prospective study was carried out by European clinical centers to evaluate the benefit of implantable cardioverter-defibrillators (ICDs) in the primary prevention of sudden cardiac death in patients carrying lamin A/C gene mutation (257). Among 19 patients implanted with an ICD and followed up to 3 yr, 8 patients

(42%) received appropriate ICD therapy to prevent ventricular arrhythmias, thus clearly demonstrating the efficacy of ICD implantation in such patients. The implantation of an ICD, rather than a pacemaker, should be considered for these patients (257). However, ICD therapy does not stop the progression of the cardiac disease in these patients. DCM often progresses until final stage of heart failure and usually requires heart transplantation.

B. Peripheral Nerve Involvement

1. Autosomal recessive Charcot-Marie-Tooth type 2 (AR-CMT2) (CMT2B1)

Charcot-Marie-Tooth disease (CMT) constitutes a clinically and genetically heterogeneous group of hereditary motor and sensory neuropathies. On the basis of electrophysiological criteria, CMT are divided into two major types: type 1, the demyelinating forms, characterized by a motor median nerve conduction velocity <38 m/s; and type 2, the axonal form, with a normal or slightly reduced nerve conduction velocity.

The first description of CMT2B1 was in a large consanguineous Moroccan family with autosomal recessive CMT2, nine affected sibs presented the onset of the clinical features in the second decade of life. All affected individuals had weakness and wasting of the distal lower limb muscles and lower limb areflexia; pes cavus was present in seven patients, and there was a proximal muscle involvement in six. Motor nerve conduction velocities were normal or slightly reduced in all patients, reflecting an axonal process (28, 214). A genome-wide search showed linkage of the disorder to markers on chromosome 1q21.2-q21.3 (28). In a separate study, three consanguineous Algerian families with autosomal recessive CMT2 were linked to chromosome 1q21 (83). A unique and founder homozygous mutation was found in the *LMNA* gene (R298C). An animal model has revealed that *Lmna* null mice presented with axonal clinical and pathological phenotype highly similar to patients with autosomal recessive CMT2 (55, 83). Later, the study of 21 AR-CMT2 patients from 7 unrelated Algerian families with the same R298C *LMNA* mutation confirmed the marked variability of the phenotype in terms of age of onset and the course severity. The presence of proximal muscle involvement in several cases seems to be a good clinical marker to identify such AR-CMT2 forms (365).

2. Autosomal dominant axonal Charcot-Marie-Tooth disease (AD-CMT2)

In addition to the AR-CMT2, *LMNA* has been also implicated as the causing mutated gene in three families with autosomal dominant form of CMT2 associated with

muscular dystrophy, cardiac disease, and leukonychia in one family (137) as well as cardiac disease and partial lipodystrophy in the two others (13, 137) (for more details, see sect. viE).

C. Partial Lipodystrophies and Related Disorders

The lipodystrophies are rare conditions characterized by selective and variable loss of adipose tissue. Metabolic complications including insulin resistance, diabetes mellitus, hypertriglyceridemia, and liver steatosis increase in severity with the extent of fat loss (for review, see Ref. 124). They can be familial or acquired. The familial types are divided into two major subtypes: congenital generalized lipodystrophies with near-complete lack of metabolically active adipose tissue from birth and familial partial lipodystrophy of Dunnigan type (FPLD), an autosomal dominant disorder. This latter form is due to *LMNA* gene mutations.

1. FPLD

Patients with partial lipodystrophy have a normal fat distribution in early childhood, but with the onset of puberty, almost all subcutaneous adipose tissue from the upper and lower extremities and gluteal and truncal areas gradually disappears, causing prominence of muscles and superficial veins in these areas. Simultaneously, adipose tissue accumulates on the face and neck, causing a double chin and fat neck. Adipose tissue may also accumulate in the axillae, back, labia majora, and intra-abdominal region. Affected patients are insulin resistant and may develop glucose intolerance and diabetes mellitus after the age of 20 yr, with hypertriglyceridemia and low levels of high-density lipoprotein (HDL). The phenotype is readily discernible in females (Fig. 10, *G* and *H*). Affected males, however, are more difficult to recognize due to relative muscularity and reduced body fat in normal individuals, accounting for the past suggestion of X-linked dominant inheritance of this disorder (89). Other pedigrees showed clear autosomal dominant inheritance (182, 303, 314). It was uncertain whether there was a distinct Koberling variety of familial lipodystrophy, which had been characterized as having loss of subcutaneous adipose tissue limited to the limbs without involvement of the trunk and with normal facial fat (202, 203).

To investigate whether there was a unique pattern of fat distribution in men and women with FPLD, whole body MRI in one male and three female patients from two pedigrees confirmed the clinical findings of near-total absence of subcutaneous fat from all extremities. Reduction in subcutaneous adipose tissue from the truncal area was more prominent anteriorly than posteriorly. Increased fat stores were observed in the neck and face. It was then concluded that FPLD results in a characteristic absence

of subcutaneous fat from the extremities, with preservation of intermuscular fat stores (126). Anthropometric variables and prevalence of diabetes mellitus, dyslipidemia, hypertension, and atherosclerotic vascular disease were assessed among 17 postpubertal males and 22 females with FPLD from 8 pedigrees. All individuals were analyzed for glucose, insulin, and lipoprotein concentrations and presented similar patterns of fat loss. Compared with the affected men, women had a higher prevalence of diabetes (50% women vs. 18% men) and atherosclerotic vascular disease (45% women vs. 12% men) and had higher serum triglycerides and lower HDL cholesterol concentrations. The prevalence of hypertension and fasting serum insulin concentrations were similar, suggesting that females with FPLD are more severely affected with metabolic complications of insulin resistance than males (123). Genome wide-scan studies as well as linkage and haplotype analysis provided conclusive evidence of linkage to 1q21-q22 locus (4, 303). *LMNA* was considered to be a candidate gene for FPLD for several reasons: FPLD maps to the same region of chromosome 1 as *LMNA*, mutations in which cause muscle wasting in AD-EDMD; and AD-EDMD regional muscle wasting is analogous to the regional adipocyte degeneration in FPLD. DNA sequencing of *LMNA* in five Canadian families affected by FPLD identified a R482G missense mutation (49, 333). To date, the majority of *LMNA* mutations associated with partial lipodystrophy of Dunnigan type are confined to those affecting the R482 amino acid (R482W, R482Q, and R482L) (385). Interestingly, in search for any relation between phenotypes and genotypes, *LMNA* mutations affecting the COOH-terminal Ig-like domain of lamin A/C were analyzed for their location on the three-dimensional structure of this domain. This analysis reveals that the mutations leading to striated muscle laminopathies affected residues localized inside the Ig domain, whereas mutations leading to partial lipodystrophy affected residues localized at the surface of this domain, highly suggesting different pathomechanisms (205).

2. Polycystic ovary syndrome and insulin resistance without lipodystrophy

Polycystic ovary syndrome with severe hyperandrogenism, acanthosis nigricans, and marked insulin resistance is a heterogeneous genetic disorder and defines the type A insulin resistance syndrome. Some cases are due to insulin receptor gene mutations (266). A unique *LMNA* mutation (G602S) was reported in a family in which the index case was a nonobese 24-yr-old woman (413). Her skin fibroblasts exhibited nuclear alterations similar to those described in other laminopathies and showed several defects in the insulin transduction pathway.

D. Systemic Laminopathies: Premature Ageing Syndromes

1. Mandibuloacral dysplasia

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive disorder characterized by postnatal growth retardation, mandibular and clavicular acroosteolysis, delayed closure of the cranial suture, joint contractures, lipodystrophy, and mottled cutaneous pigmentation. (53, 114, 340, 414).

Partial lipodystrophy, extreme insulin resistance, and marked hypermetabolism have been observed in MAD patients. Studies of body fat distribution in two male and two female patients with MAD found that three of the four subjects had loss of subcutaneous fat from the extremities with normal or slight excess in the neck and truncal regions (pattern A). In contrast, one patient had generalized loss of subcutaneous fat involving the face, trunk, and extremities (pattern B). All of the patients had normal glucose tolerance, but fasting and postprandial hyperinsulinemia were suggestive of insulin resistance. Therefore, there are two types of body fat distribution patterns, both of which are associated with insulin resistance and its metabolic complications (71, 114, 340). By analysis of five consanguineous Italian families, a linkage of MAD to 1q21 was found; DNA sequencing of the *LMNA* gene identified a homozygous mutation (R527H) in the families, and patient skin fibroblasts showed abnormal lamins A/C distribution and dysmorphic nuclear envelope (285). Further mutational analysis of *LMNA* in MAD patients from six pedigrees found that patients from two pedigrees with pattern A lipodystrophy had the homozygous R527H *LMNA* mutation, whereas the other four affected subjects, who had pattern B lipodystrophy, did not have any mutation in the exons or splice junctions of the *LMNA* gene (339). In the remaining patients, sequencing of other genes implicated in lipodystrophies does not reveal any substantial alterations (339), suggesting genetic heterogeneity of MAD. This was confirmed by identifying mutations in the *ZMPSTE24* gene, also known as *FACE-1* in human, in the remaining four patients (2). More recently, a novel homozygous A529V *LMNA* mutation was identified in Turkish patients with MAD phenotype with subtle differences in phenotype compared with those with the classical R527H MAD mutation (125).

2. Hutchinson-Gilford progeria syndrome

Hutchinson-Gilford progeria syndrome (HGPS) is an exceedingly rare fatal genetic disorder first reported by Hutchinson and Gilford (134, 174) characterized by precocious appearance of senility of a striking degree. The estimated incidence is one in eight million births. The inheritance pattern, paternal age effect, and lack of consanguinity argue that it is due to a sporadic dominant

mutation. Children with HGPS appear healthy at birth. Clinical features appear within the first few years of life, including severe growth retardation with short stature and lower weight for height; delayed anterior fontanel closure; incomplete sexual maturation; widespread atherosclerosis of aorta, coronary, and cerebral arteries; loss of subcutaneous fat; craniofacial abnormalities with micrognathia; prominent eyes; a beaked nose; alopecia; restricted joint mobility; and other skeletal abnormalities including coxa valga, delayed and crowded dentition, thin and high pitched voice, pyriform thorax, short dystrophic clavicles, and diminished subcutaneous fat, prominent scalp veins, and dystrophic nails. The bones might show distinctive changes, resorption of clavicles and replacement by fibrous tissue, as well as resorption of terminal phalanges (acro-osteolysis). Aseptic necrosis of the head of the femur and hip dislocation are also common. Mental and emotional developments are normal. According to reviews of the literature, the age at death ranges between 7 and 27.5 yr, with a median age of 13.4 yr, and death occurs frequently from coronary artery disease (for review, see Ref. 75).

Cytogenetical analysis showed an inverted insertion in the long arm of chromosome 1 in 70% of the cells, suggesting that a gene for progeria might be located on chromosome 1 (43). In a 9-yr-old patient with a classic picture of Hutchinson-Gilford progeria, an interstitial deletion on region 1q23 was found (81). Positional cloning and candidate gene approaches had both led at the same time to the identification of a de novo single-base substitution (c.1824C>T) resulting in a silent change within exon 11 (p.G608G) to be responsible for HGPS (82, 97). This mutation was shown to activate a cryptic splice site within *LMNA* exon 11, resulting in an in-frame deletion of 50 amino acids within the COOH-terminal end of the prelamin A. This abnormal prelamin A, also termed progerin, still retains the CaaX box but lacks the site for endoproteolytic cleavage. Immunofluorescence analyses of HGPS fibroblasts and lymphoblasts with antibodies directed against lamin A revealed that many cells showed nuclear abnormalities including altered nuclear sizes and shapes as well as nuclear envelope interruptions accompanied by chromatin extrusion (97). Lamin A was detected in 10–20% of HPGS cells. Only lamin C was present in most cells, and lamin B1 was found in the nucleoplasm, suggesting that it had dissociated from the nuclear envelope. Western blot analysis showed 25% of normal lamin A levels, and no truncated form was detected (82).

Seven different other *LMNA* mutations have been also reported in HGPS including one homozygous and compound heterozygous mutations (48, 82, 116, 306, 405) (for a complete list, see UMD-*LMNA* mutation database at www.umd.be:2000).

3. Atypical Werner syndrome

Werner syndrome is characterized clinically by the premature appearance of features associated with normal ageing and cancer predisposition. Individuals with Werner syndrome develop normally until the end of the first decade. Symptoms typically start in the second to third decades. The main clinical features of Werner syndrome are scleroderma-like skin changes, especially in the extremities (tight and atrophic skin, pigmentary alterations, ulceration, hyperkeratosis, regional subcutaneous atrophy), bilateral cataract, short stature, subcutaneous calcification, premature arteriosclerosis, diabetes mellitus, hypogonadism, osteoporosis, soft tissue calcification, osteosclerosis of distal phalanges of fingers and/or toes, neoplasms (sarcomas), abnormal voice, wizened-prematurely aged face (birdlike faces), and premature graying and/or thinning of scalp hair. Among the laboratory testing, urinary and serum concentrations of hyaluronic acid are increased in most individuals with Werner syndrome (for review, see Ref. 75). Werner syndrome has been found to be caused by mutations in the DNA helicase-like (*RECQL2*) gene, which encodes a homolog of the *Escherichia coli* RecQ helicase (416). However, several patients had a phenotype classified as “atypical Werner syndrome,” with a more severe phenotype than that observed with mutations in the *RECQL2* gene. In an extended study of 129 indexed patients referred to the international registry for molecular diagnosis of Werner syndrome, 26 were categorized as having atypical Werner syndrome on the basis of molecular criteria (60). In these individuals, DNA sequencing of all exons of the *LMNA* gene revealed that four patients were heterozygous for novel missense mutations in this gene. Fibroblasts from one patient had a substantially enhanced proportion of nuclei with altered morphology and mislocalized lamins (60). These atypical Werner syndrome patients with *LMNA* mutations had a more severe phenotype than did those with the disorder due to *RECQL2* mutations. However, the clinical designation of “atypical” Werner syndrome for the four *LMNA* mutated patients described by Chen et al. (60) appeared somewhat insecure and is still a matter of debate (see sect. viD4) (24, 159, 386).

4. Generalized lipoatrophy, insulin-resistant diabetes, leukomelanodermic papules, liver steatosis, and hypertrophic cardiomyopathy (LIRLLC)

A peculiar form of lipoatrophy with diabetes was described in a 27-yr-old male patient whose phenotype was characterized by acquired generalized lipoatrophy with metabolic alterations, massive liver steatosis, distinctive subcutaneous manifestations, and cardiac abnormalities involving both endocardium and myocardium (52). Generalized atrophy of subcutaneous fat resulted in sunken cheeks and muscular pseudohypertrophy of the

four limbs. Multiple whitish papules on pigmented skin were present on the neck, trunk, and upper limbs and to a lesser extent on the lower limbs. Muscular strength was normal, and no neurological defects were detected. Cardiac involvement included concentric hypertrophy of the left ventricle without cavity dilatation associated with thickness and regurgitant valves, aortic fibrotic nodules, and calcification of the posterior annulus. Doppler echocardiographic findings were similar to those described in aged patients. Abdominal MRI revealed an absence of body at both the subcutaneous and visceral levels. Family members were unaffected, and no consanguinity was reported. Mutation analysis of *LMNA* found a heterozygous mutation R133L in the rod domain of lamins A and C (52). Accordingly, nuclear abnormalities in primary cultures of patient fibroblasts were observed (52).

Interestingly, the mutation found in this patient with LIRLLC was secondarily reported in two others suffering from the atypical Werner syndrome (60). The highly similar clinical features of these three patients strongly suggest that the phenotype of the two atypical Werner syndrome patients may be only a variant of the LIRLLC syndrome (24, 159, 386).

5. Restrictive dermopathy

Restrictive dermopathy (RD), also known as tight skin contracture syndrome, is a rare disorder mainly characterized by intrauterine growth retardation, tight and rigid skin with erosions, prominent superficial vasculature and epidermal hyperkeratosis, facial features (small mouth, small pinched nose and micrognathia), sparse or absent eyelashes and eyebrows, mineralization defects of the skull, thin dysplastic clavicles, pulmonary hypoplasia, multiple joint contractures, and an early neonatal lethal course within the first week of life. In a recent study of nine cases with RD, two were found to carry heterozygous splicing mutation in the *LMNA* gene, leading to the complete or partial in-frame loss of exon 11 in mRNAs encoding lamin A and resulting in a truncated prelamin A (278). The remaining cases were found to carry a unique mutation in the *ZMPSTE24* (*FACE-1*) gene (see sect. viF).

6. Lethal fetal akinesia

A case of a newborn deceased child with a homozygous *LMNA* nonsense mutation (Y259X) was recently described. He showed a lethal phenotype including dysmaturity, facial dysmorphism with retrognathia, severe contractures of the fingers and the toes, long-bone fractures, and severe generalized muscular dystrophy with an almost complete absence of fibers in intercostal muscles. He died from respiratory insufficiency soon after premature birth at 30 wk of gestation. His two parents were first cousins of a large Dutch family with LGMD1B; they carry the Y259X *LMNA* mutation at heterozygous state (267,

378). Cultured cells from skin fibroblast of this child showed severe nuclear abnormalities in the absence of A-type lamins: nuclear blebbing and protrusion of DNA into the cytoplasm, local absence of lamin B, and NPCs, as well as a largely reduced level of emerin staining at the nuclear membrane area (Fig. 11, see also Ref. 271).

E. Overlapping Laminopathies: A Still Extending Class

There are an increasing number of publications reporting isolated or familial cases harboring several tissue involvements and suggesting a real overlapping continuum within the different types of laminopathies.

1. Muscular dystrophy, dilated cardiomyopathy, and partial lipodystrophy

Several patients with clinical features of lipodystrophy, carrying one of the following heterozygous *LMNA* mutations, R28W, R60G, R62G, R527P, or the typical R482W FPLD mutations, were reported to present also variable combinations of cardiac and/or skeletal muscular alterations of various severity (127, 375, 379). These reports highlight the importance of careful neuromuscular and cardiac investigations in PLD patients, even in those bearing the typical *LMNA* R482W mutation.

2. AD-CMT2 associated with muscular dystrophy, cardiac disease, and leukonychia

A unique *LMNA* mutation (E33D) was identified in a father and his daughter belonging to a large family clinically characterized by the combination of axonal neuropathy with myopathic features, cardiac disease including DCM, conduction disturbances and arrhythmia, and leukonychia (137). More recently, the detailed nerve lesions of the index patient of this family were reported (387). Neurogenic and myogenic patterns coexisted on muscle biopsy specimens, whereas the peripheral nerve presented a mixture of axonopathy and Schwann cell hypertrophy even if the axonal damage was predominant. Thus *LMNA* represents the first gene implicated in both recessive and dominant forms of CMT2.

3. AD-CMT2 associated with myopathy and/or partial lipodystrophic features

There was another unique report of a family in which two patients showed evidence for axonal neuropathy and partial lipodystrophy in the mother as well as axonal neuropathy associated with scapuloperoneal myopathy and partial lipodystrophy in the son. In the latter, muscle biopsy revealed myopathic and neurogenic features including atrophic fibers, few necrotic fibers, increased connective tissue, and fiber-type grouping. Nerve biopsy

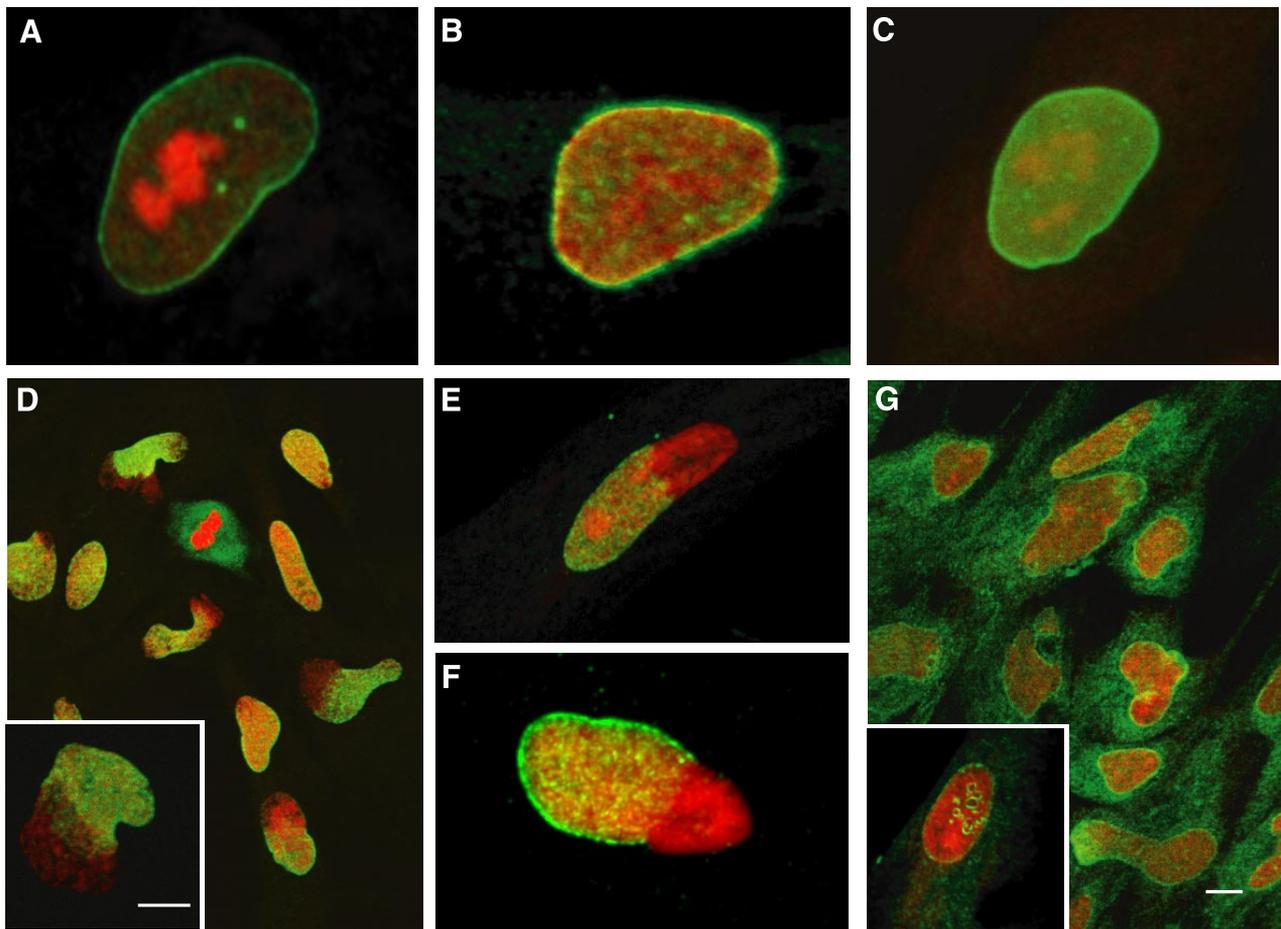


FIG. 11. Micrographs of normal (A–C) and laminopathy (D–G) human fibroblasts. Cells were immunostained with FITC-conjugated antibodies (green) and counterstained with propidium iodide (red). A: lamin B1. B: the nuclear pore complex protein p62. C: emerin. Cultured fibroblasts from a patient with lethal homozygous *LMNA* mutation (Y259X) that were null for lamins A/C were immunostained with antibodies to lamin B2 (D), the nuclear pore complex protein p62 (E), lamin B1 (F), and emerin (G). Note the abnormal shape of the nuclei and the discontinuous abnormal localization of the lamin-associated proteins in the laminopathy cells.

showed axonal loss of primarily large and medium-sized myelinated fibers and rare abnormally thick myelin sheath or small onion bulbs (13). Screening of the *LMNA* gene identified a R571C mutation in the lamin C specific tail domain. The authors suggested a possible common etiology for the muscle and nerve involvements in this family (13). Interestingly, the same mutation R571C was previously reported in a family with isolated DCM and conduction system defects (99).

4. Progeroid syndrome and myopathy combination

The case of a young girl with a phenotype combining early-onset myopathy and a progeria was recently reported (198). The myopathy onset was in the first year of life. Typical progeroid features developed later. A missense *LMNA* mutation (S143F) was identified. This was the first report of a patient combining progeria and myopathy features.

F. Other Nuclear Envelopathies

1. Secondary laminopathies: FACE1/ZMPSTE24-related disorders

FACE-1 is the human gene encoding a metalloproteinase Face-1 (also called ZMPSTE24) involved in prelamins A posttranslational processing of the extreme COOH-terminal residues (see sect. II C). The first mutations in this gene have been reported in MAD patients in whom no *LMNA* mutation was found (2). The rationale for testing *FACE-1* in these patients was the fact that mice with homozygous deletion of *Zmpste24* gene (the mouse homolog gene of *FACE-1*) exhibit MAD features (15, 300). After this, mutations of *Face-1* were reported in neonates showing the restrictive dermopathy phenotype (277, 278). The authors found a complete absence of both Face-1 and mature lamin A associated with prelamins A accumulation, suggesting that *FACE1/ZMPSTE24*-related disorders can be considered as secondary laminopathies (277).

2. *LBR*-related disorders

Heterozygous null mutations in the gene encoding the lamin B receptor gene have been identified in patients showing specific altered nuclear morphology in granulocytes observed in Pelger-Huët anomaly (PHA) (166). The PHA is a benign autosomal dominant disorder characterized by abnormal nuclear shape and chromatin organization in blood granulocytes. Affected individuals show hypolobulated neutrophil nuclei with coarse chromatin of granulocytes. Later on, homozygous mutations in *LBR* were also identified in patients presenting a Greenberg skeletal dysplasia phenotype known also as Hydrops-ectopic calcification-“moth-eaten” (HEM) skeletal dysplasia (395). This latter autosomal recessive in utero lethal disease is characterized by chondrodystrophy with a lethal course, fetal hydrops, short limbs, and abnormal chondro-osseous calcification. PHA and Greenberg skeletal dysplasia are allelic disorders both due to nonsense or truncating mutations leading to various degrees of haploinsufficiency in relation to their mode of inheritance: AD versus AR, respectively (166, 395). Mouse studies suggest that PHA and Greenberg/HEM dysplasia may represent the extremes of a single clinical spectrum ranging from one similar to PHA, to alopecia, variable expression of syndactily, and hydrocephalus and skeletal abnormalities (336).

3. *MAN1*-related disorders

Mutations in *LEMD3*, the gene encoding *MAN1*, have been identified in a constellation of autosomal dominant allelic disorders characterized by increased bone density (163), including osteopoikilosis, Buschke-Ollendorff syndrome, and melorheostosis. These conditions are paucisymptomatic or may manifest with chronic pain in the affected limbs.

4. *NPC* protein-related disorders

Some NPC proteins are involved in acquired or hereditary human diseases (for review, see Ref. 69). In addition to the relationships between NPC proteins and primary biliary cirrhosis, some cancer varieties, and viral infections, the triple A syndrome is caused by mutations in the *AAAS* gene that encodes a protein, *ALADIN* (for alacrima-achalasia-adrenal insufficiency neurological disorder) (149, 372), localized to NPC (68). Triple A syndrome (also called Allgrove syndrome) is a rare, autosomal, recessive disease clinically characterized by four major features including adrenocorticotrophic hormone-resistant adrenal insufficiency, achalasia, alacrima, and some inconstant neurological symptoms often involving the autonomic nervous system. The disease expression is usually variable in terms of age of onset and symptom severity. As the exact pathogenesis of the disease is still unknown, the treatment is mainly symptomatic.

VIII: MOLECULAR MECHANISMS UNDERLYING LAMINOPATHY AND NUCLEAR ENVELOPATHY

A number of hypotheses have been proposed that have attempted to link the pathophysiology of laminopathy and nuclear envelope diseases to known or emerging functions of lamins and NETs (Fig. 12). These include ideas surrounding the role of lamins and NETs in maintaining the mechanical integrity of cells (the structural hypothesis), the role of lamins and NETs in transcription and cell signaling (the gene expression hypothesis), and emerging roles of lamins in adult stem cell differentiation and cellular ageing (the cell proliferation theory). While at face value each hypothesis appears different and might explain different aspects of each disease or different diseases, it is worth keeping in mind that all functions of lamins are dependent on their ability to anchor multiprotein complexes to the NE or to sites within the nucleoplasm. As such, none of the theories can be viewed as mutually exclusive.

A. The Structural Hypothesis

The structural hypothesis proposes that one of the most important functions of the lamina is to maintain the structural integrity of cells, particularly cells subjected to mechanical load. Loss of lamin or NET function as a result of mutation leads to weakness in the cell, and this in turn leads to death when cells are subjected to stress

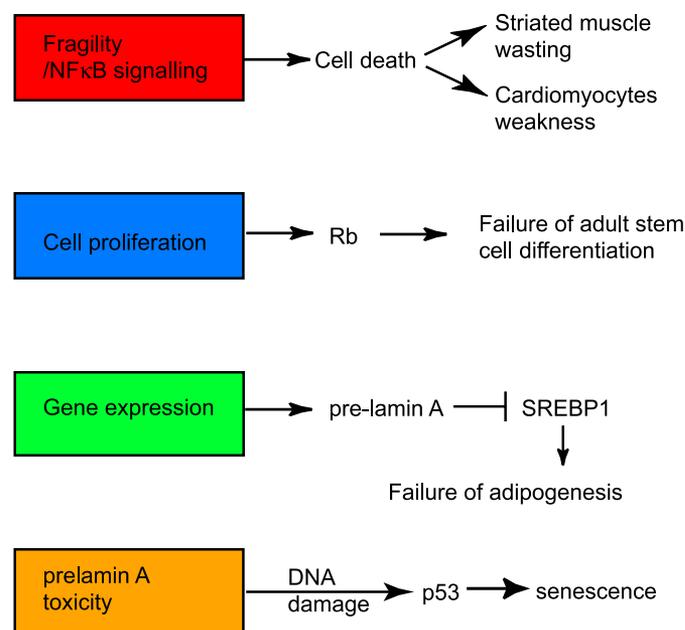


FIG. 12. Summary diagram indicating the potential routes of development of laminopathies. Most likely a combination of these processes leads to the different clinical phenotypes.

(176). There is now considerable evidence to support this hypothesis. A consistent feature of cells obtained from laminopathy patients is evidence of mechanical damage to the NE. This is manifested by abnormally shaped NEs (termed herniations) or holes in the NE (termed honeycomb structures). Moreover, these abnormalities accumulate with age (31, 83, 140, 270, 271, 278, 384). The NE abnormalities probably arise because mutated lamins form unstable associations with the lamina (38, 290, 311, 384).

While those mutations in the rod domain found in laminopathy patients investigated until now are not predicted to alter lamin dimerization significantly, higher order assembly or interaction of lamins with associated proteins could be affected (356). Mutations in the Ig-fold can either affect head-to-tail polymerization or interaction of lamins with other proteins. A single point mutation (R453W), occurring in EDMD, causes a dramatic destabilization of the three-dimensional structure of the COOH-terminal domain of lamin A/C (205). Dramatic structural changes are not observed in a common FPLD mutation, R482W, but the suppression of the positive charge of this particular region alters the binding characteristics of these molecules to DNA (354).

Moreover, possibly due to the fact that lamins form obligate dimers or because mutant lamins are more stable and accumulate with age, the mutant lamins exert a dominant effect over their wild-type counterparts (140). Loss of stability of lamins within the lamina also arises in cells from X-EDMD patients that are null for emerin, and this also results in structural abnormality (248).

Three studies have now revealed that loss of lamina integrity has a direct influence on the physical integrity of cells and therefore their ability to tolerate mechanical strain. Using biomechanical techniques, two groups have shown that in embryonic fibroblasts (MEFs) from a *Lmna* $-/-$ mouse the NE is significantly weaker than in MEFs from *Lmna* $+/+$ littermates. This weakness has two important consequences. First, the *Lmna* $-/-$ MEFs are unable to resist forces of compression and are ruptured more easily when subjected to physical loads (38). Second, the NF κ B-regulated stress response pathway is abrogated and *Lmna* $-/-$ MEFs die after physical perturbations that are not lethal in *Lmna* $+/+$ MEFs (208). Emerin $-/-$ MEFs also display mechanical weakness within the NE and abrogation of the NF κ B pathway, but to a lesser extent than in *Lmna* $-/-$ MEFs (207). It is generally accepted that loss of physical integrity is probably a cause of cell death in the striated muscle disorders. Evidence for physical damage in both cardiac and skeletal muscle has been reported in both *Lmna* mouse models of DCM (268, 282) or EDMD (7), in skeletal muscle biopsy from X-EDMD and AD-EDMD patients (103, 248), and in cardiac biopsies from patients with DCM (6). The damage includes ruptured NEs and leakage of chromatin into the

cytoplasm, which is thought to arise because the weakened NE breaks apart in contractile tissues. In skeletal muscle, presumably some broken nuclei can be tolerated because each muscle fiber is a syncytium containing many nuclei. However, in cardiomyocytes, any rupture of the NE is likely to be lethal, and this probably explains why in the striated muscle disorders, muscle weakness and wasting progress slowly, but the life-threatening condition is sudden heart failure (373).

Loss of lamin A/C function not only gives rise to mechanical weakness within the cell but also results in disorganization of all the elements of the cytoskeleton (38), probably because the nesprins become mislocalized to the ER (220, 271, 419). Cytoskeleton disorganization may also compromise striated muscle function, and indeed, desmin filaments are completely disrupted in cardiomyocytes from *Lmna* $-/-$ mice (268, 282). Disruption of cytoskeleton organization might also underlie certain aspects of CMT disorder. It has recently been shown that nesprin-1 is required for positioning of nuclei at the postsynaptic membrane of muscle cells at neuromuscular junctions (143). The nuclei positioned at the postsynaptic membrane transcribe genes required for synaptic function. While it is clear that positioning of nuclei is not required for maturation of the neuromuscular junction (143), a lack of specialized nuclei might give rise to loss of synaptic function later in life.

B. The Gene Expression Hypothesis

While it is generally agreed that loss of structural integrity can explain many features of the striated muscle disorders, it is much more difficult to understand how mechanical weakness could cause white fat disorders. Therefore, it has been proposed that altered patterns of gene expression in the presence of laminopathy mutations might be the underlying causes of these diseases (62). Adipogenesis is regulated by a number of genes including SREBP1, peroxisome proliferator activator receptor gamma (PPAR γ), and Rb. While Rb is required for cell cycle arrest and promotion of early differentiation events (63, 313), PPAR γ is pivotal to the activation of adipogenic genes (3). PPAR γ is itself activated by SREBP1 (197) and has been identified as a lamin A binding protein in yeast two-hybrid screens (229). It has now been reported that prelamin A and not mature lamin A is the *in vivo* binding partner of SREBP1. Moreover, in fibroblasts from FPLD, MAD, and atypical Werner's patients, prelamin A accumulates at the NE, and this in turn results in sequestration of SREBP1 to the NE. Sequestration of SREBP1 to the NE has been proposed to reduce the pool available for activation of PPAR γ and therefore to inhibit adipogenesis (50). In many ways loss of SREBP1 activity as a result of prelamin A accumulation is an

attractive model that could explain a number of features of FPLD and MAD. For example, it has been shown that accumulation of the classical HGPS lamin A mutation, that retains the prelamin A tail, within the NE is age dependent (140), and this might explain the late onset of loss of white fat. In addition, loss of SREBP1 has been generally correlated with type II diabetes within United Kingdom populations (332). However, while loss of SREBP1 function might explain the loss of white fat throughout the trunk, it is harder to see how this could account for accumulation of white fat around the neck or the androgenic features of female patients. Loss of Rb function as a result of A-type lamin defects (186) would also be predicted to result in a failure of adipogenesis (63); however, there is as yet no evidence to support such a model.

C. The Cell Proliferation Theory

Loss of Rb function has been investigated in relation to lamin function in adult skeletal muscle stem cell (satellite cell) differentiation. Lamina organization has been shown to be important for satellite stem cell differentiation in a number of studies. With the use of a monoclonal antibody that specifically detects lamin A that is associated with nuclear speckles (183), it has been reported that during myoblast differentiation, epitope masking of lamin A occurs within the speckles as a result of cyclin D-dependent sequestration of Rb (272, 273). Moreover, a dominant lamin A mutant that prevents the association of wild-type lamin A with speckles inhibits myoblast differentiation (245). This finding has led to the proposal that the lamin-mediated sequestration of Rb to speckles is necessary for the differentiation of satellite cells. Other studies have revealed that differentiation of mouse satellite cells is also accompanied by relocation of nucleoplasmic lamin A and C to the nuclear lamina and reorganization of the LAP2 α nucleoskeleton (247). AD-EDMD causing lamin A mutations prevent this reorganization of the lamina and nucleoskeleton and as a result inhibit satellite cell differentiation (247) but promote apoptosis (101). Moreover, failure of satellite cell differentiation is correlated with loss of expression of Rb (247), possibly resulting from proteasomal destruction (186). The finding that AD-EDMD mutations prevent satellite cell differentiation correlates well with the observation that EDMD patients have little or no capacity to regenerate skeletal muscle (331). These findings have led to the suggestion that the EDMD phenotype can be explained by both nuclear fragility leading to cell death that eventually gives rise to heart failure and also because a failure of adult stem cell differentiation prevents regeneration of skeletal muscle and possibly cardiac muscle (177).

The finding that AD-EDMD mutations promote apoptosis (101) has given rise to a more general hypothesis

that many features of laminopathy disease are explained by abnormally regulated cell proliferation and cell death. Fibroblasts from HGPS patients display abnormally high cell proliferation indexes at early passage but increased rates of apoptosis. However, this rapid growth/apoptotic phenotype gives way to premature cellular senescence at later passage number (31). In contrast to *Lmna* $-/-$ MEFs, the fibroblasts from a unique individual with a lethal homozygous *LMNA* mutation Y259X that were null for lamins A/C grow very slowly in culture and also senesced prematurely (271, 378). Skin fibroblasts from a mouse model of progeria (267) also undergo premature cellular senescence. If skin fibroblasts represent models for the proliferative capacity of adult stem cells, then one explanation of ageing phenotypes associated with the most severe laminopathies is that the mutated lamins impose a senescent phenotype on adult stem cells that prevents their amplification and therefore limits their capacity for regeneration.

D. Prelamin A Toxicity

In the most severe laminopathy diseases, forms of prelamin A accumulate within the NE either because activation of a cryptic splice donor site generates a truncated form of prelamin A (called progerin) that lacks the endoproteolytic cleavage site needed for lamin A maturation (97) or because of FACE-1/*Zmpste24* deficiency, which results in the accumulation of a partially processed prelamin A product in the NE (15, 277, 300, 334). *Zmpste24* $-/-$ mice have provided an invaluable model to understand the consequences of accumulation of partially processed prelamin A. This prelamin A is isoprenylated and carboxymethylated, but subsequent cleavage of the aaX peptides and the isoprene group does not take place. *Zmpste24* $-/-$ mice display many features of progeria including growth retardation, alopecia, micrognathia, osteolytic lesions, and osteoporosis. Moreover, the *Zmpste24* deficiency is clearly linked to the accumulation of this partially processed prelamin A within the NE (15, 300). Accumulation of partially processed prelamin A in the NE has been proposed to be toxic in certain cells, and direct evidence for this hypothesis has now been reported. In one study the *Zmpste24* $-/-$ mouse was crossed with a *Lmna* $+/-$ mouse to produce a *Zmpste24* $-/-$ *Lmna* $+/-$ genotype. This mouse was predicted to be haploinsufficient for *Lmna*, and indeed, fibroblasts from this mouse expressed significantly less prelamin A than its *Zmpste24* $-/-$ *Lmna* $+/+$ counterpart. Strikingly, *Zmpste24* $-/-$ *Lmna* $+/-$ were phenotypically normal, suggesting that a 50% reduction in the level of expression of partially processed prelamin A is sufficient for protection against disease (111). Later studies showed that only partially processed prelamin A is

toxic to cells, while completely unprocessed prelamin A (which is not isoprenylated, preventing further processing steps) seems to be less damaging to cells. Unprocessed prelamin A in general accumulates in intranuclear aggregates and apparently does not interfere with normal lamins in the formation of the lamina. In contrast, the partially processed prelamin A of *Zmpste24*^{-/-} cells accumulates at the nuclear lamina, interfering with normal lamina polymer formation, causing, among others, nuclear blebbing. When these cells are treated with farnesyl transferase inhibitors (FTI), preventing the first processing step, a normalization of nuclear shape can be detected. (371). These findings were confirmed in HeLa cells transfected with prelamin A constructs containing mutations that prevent cleavage by *Zmpste24*^{-/-} (235). While expression of this mutant lamin A induced nuclear abnormalities, treatment with FTI normalized nuclear shape. Also, cells transfected with progerin and showing abnormally shaped nuclei could regain normal nuclear shape by treatment with FTI (51). Similar findings were observed after FTI treatment of fibroblast cultures from HGPS patients (371) or from mouse fibroblasts with a targeted HGPS mutation (409). In an independent investigation, *Zmpste24* was eliminated from HeLa cells using siRNA. Elimination of *Zmpste24* led to accumulation of partially processed prelamin A at the NE and within intranuclear dots and resulted in cell cycle arrest and apoptosis, again suggesting that accumulation of this form of prelamin A is toxic (145). In a mouse model mimicking HGPS, treatment of affected cells with farnesyl transferase inhibitors results in improvement of nuclear shape, similar to patient fibroblasts. Moreover, the FTI-treated mice exhibited improved body weight, grip strength, bone integrity, and prolonged survival (109).

While treatment with FTI results in the normalization of nuclear shape, this does not necessarily imply that all nuclear functions are restored in these cells. Mechanical cellular weakness (38) as well as impaired mechanotransduction (208) result from the absence of A-type lamins rather than incorrect processing. Thus FTI treatment might induce mechanical weakness in cells by reducing the amount of mature lamin A. Moreover, very little is known about the number of other proteins present in human cells, which require farnesylation for proper functioning. Very recently, a new inner nuclear membrane protein Kugelkern was discovered in *Drosophila*, which is important for maintaining nuclear size and requires farnesylation of the CaaX motif for incorporation into the nuclear membrane (29). More promising seems to be the approach in which only the mRNA and protein product of the modified lamin A was eliminated from HGPS fibroblasts using a modified oligonucleotide targeted for the cryptic splice donor site in the classical HGPS mutation. Elimination of the protein rescued most of the phenotypic defects, including restoring normal nuclear

shape, and normalization of the expression of several deregulated proteins in these fibroblasts (321). Similar findings were reported with RNAi using an shRNA lamin construct (172).

The ageing phenotype in cells that accumulate prelamin A can now be explained by defective DNA repair and activation of p53 signaling. Fibroblasts and bone marrow cells from *Zmpste24*^{-/-} mice as well as HGPS fibroblasts, display increased levels of aneuploidy and DNA damage and greater sensitivity to DNA damaging agents compared with their wild-type counterparts. The increased sensitivity to DNA damaging agents is correlated with a failure to recruit p53-binding protein 1 and RAD51 to sites of DNA lesions, implying a perturbation of DNA damage response pathways (225). A general loss of function of the DNA repair machinery in laminopathies, however, seems unlikely. Patients with laminopathies other than progeria with a relatively long life expectancy do not develop cancer in more cases than expected. A recent paper by Therizols et al. (367) could explain the observed phenomenon in *Zmpste24*^{-/-} mice. They state that the correct functioning of double-strand DNA repair is dependent on correct telomere tethering to the nuclear periphery. Because peripheral chromatin organization is largely disturbed in *Zmpste24*^{-/-} mice, this could explain why DNA repair is delayed (225). Interestingly, while DNA damage response pathways are defective, p53 signaling appears to be enhanced, since p53 target genes are significantly upregulated in *Zmpste24*^{-/-} cells and tissue, but this response is abrogated in *Zmpste24*^{-/-} *Lmna*^{+/-} mice (380). Thus, while an immediate response to DNA damaging agents is defective, it appears that p53-mediated entry into a senescent program may be promoted by the presence of prelamin A, and therefore, this might be the basis of prelamin A toxicity.

IX. CONCLUSIONS

Lamins and NETs are central players in cell function. They play critical roles in organizing the cytoskeleton, in regulating gene expression, and in determining the longevity of metazoan organisms. When A-type lamins are expressed in mutant forms, particularly in forms that are only partially processed, they accelerate ageing by imposing a senescent program on dividing cells or by contributing to weakness and cell death in differentiated cells. In other models, the presence of mutated lamins impairs differentiation and therefore might influence the ability of adult stem cells to repair tissue damage or replace dead cells. It may be the case that each laminopathy is caused by a single mechanism or that certain laminopathies arise through a combination of the mechanisms described above. The challenge for the next 3 years will be to understand which of the current hypotheses applies to

which laminopathy so that appropriate strategies for treatments can be devised. Given their central role in ageing diseases, A-type lamins and their binding partners now represent key targets for new antiageing drugs.

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GRANTS

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