REVIEW

Nuclear lamins: building blocks of nuclear architecture

Robert D. Goldman,[1,3,4] Yosef Gruenbaum,[2,3] Robert D. Moir,[1] Dale K. Shumaker,[1] and Timothy P. Spann[1]

[1]Northwestern University Medical School, Department of Cell and Molecular Biology, Chicago, Illinois 60611, USA;
[2]The Hebrew University of Jerusalem, Department of Genetics, Institute of Life Sciences, Jerusalem 91904, Israel;
[3]The Marine Biological Laboratory, Woods Hole, Massachusetts 02543, USA

Nuclear lamins were initially identified as the major components of the nuclear lamina, a proteinaceous layer found at the interface between chromatin and the inner nuclear membrane (Fawcett 1966). Due to their position at the periphery of the nucleus, lamins were originally proposed to support the nuclear envelope and provide anchorage sites for chromatin. Recently, the nuclear lamins have also been found in the nucleoplasm (Fig. 1). In addition, experimental and genetic evidence suggest that nuclear lamins are involved in a number of other functions including nuclear envelope assembly, DNA synthesis, transcription, and apoptosis. Interestingly, mutations in nuclear lamins have been linked to human diseases. In this review, we describe what is known of the structure and function of lamins and their associated proteins. Further, we speculate about possible mechanisms through which mutations in nuclear lamins give rise to disease. Immunological and structural data originally suggested that the lamins were related to cytoplasmic intermediate filaments (IF) (Aebi et al. 1986; Goldman et al. 1986). The cloning and sequencing of lamin cDNAs confirmed that lamins have the typical domain structure of IF including an α-helical coiled-coil domain flanked by nonhelical domains (Fisher et al. 1986; McKeon et al. 1986). Interestingly, analyses of lamin and cytoplasmic IF genomic sequences indicate that nuclear lamins are the progenitors of all IF, with cytoplasmic IF arising through gene duplication (Riemer et al. 2000).

Structure and assembly properties of the nuclear lamins

An extensive search of the genomes of humans and other mammals reveals three lamin genes (*LMNA*, *LMNB1*, and *LMNB2*), encoding seven alternatively spliced isoforms. The A-type lamins A, AΔ10, C, and C2 are all derived from the *LMNA* gene (Fisher et al. 1986; McKeon et al. 1986; Furukawa et al. 1994; Machiels et al. 1996). The B-type lamins are B1 encoded by *LMNB1*, and B2–B3 encoded by *LMNB2* (Pollard et al. 1990; Biamonti et al. 1992; Furukawa and Hotta 1993; Stuurman et al. 1996). All vertebrate cells express at least one B-type lamin, whereas lamins A, AΔ10, and C are developmentally regulated and are expressed primarily in differentiated cells (Rober et al. 1989; Machiels et al. 1996). Lamins C2 and B3 are expressed only in germ-line cells (Furukawa and Hotta 1993; Furukawa et al. 1994; Alsheimer et al. 1999). These observations suggest cell-type and tissue-specific functions for lamins.

The number and complexity of lamin genes increased during metazoan evolution. *Caenorhabditis elegans* has only one lamin gene (*lmn-1*), which is expressed in all cells, except for mature sperm (Liu et al. 2000). *Drosophila melanogaster* has two lamin genes (Dm_0 and *C*). Lamin Dm_0 is expressed in essentially all cells throughout development, whereas *lamin C* is initially expressed late in embryonic development and in differentiated cells (Gruenbaum et al. 1988; Bossie and Sanders 1993). The genome sequences of yeast and *Arabidopsis* have revealed that these species do not have nuclear lamins, suggesting that these proteins may have evolved in animal cells during the transition from a closed to an open mitosis (Cohen et al. 2001).

The central rod domain of the lamins consists mainly of heptad repeats that are characteristic of α-helical proteins (McKeon et al. 1986; Stuurman et al. 1998). This domain drives the interaction between two lamin protein chains, to form a coiled-coil dimer, the basic structural unit of lamin assembly. Lateral associations between the rod domains of dimers are essential for the assembly of the higher order structures required for lamin polymerization (Stuurman et al. 1998). Although the central rod domain of lamins is well conserved when compared with cytoplasmic IF proteins, the lamin sequence has two distinctive features, an additional six heptads, and no stutter residues interrupting the heptad repeats (Parry et al. 1986). The rod domain is flanked by amino- and carboxy-terminal non-α-helical domains. These end domains are variable in the different lamins and they are known to play important roles in lamin assembly (Moir et al. 1991). The carboxy-terminal domain has a nuclear localization sequence (NLS) for

[4]Corresponding author.
E-MAIL r-goldman@nwu.edu; FAX (312) 503-0954.
Article and publication are at http://www.genesdev.org/cgi/doi/10.1101/gad.960502.

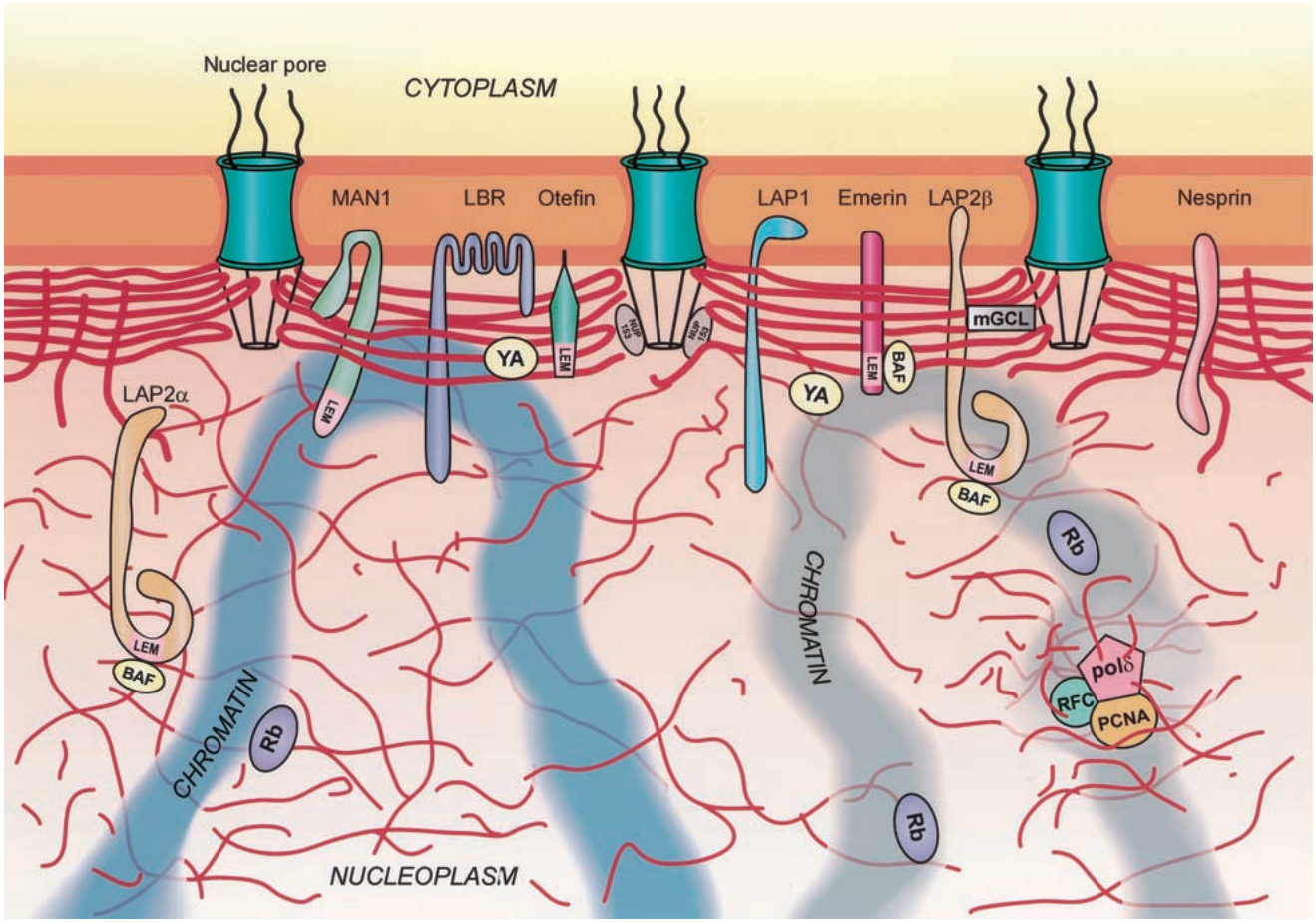

Figure 1. Illustration depicting the various proposed interactions of lamins with inner nuclear membrane proteins, nuclear pores, and various other nucleoplasmic factors. The lamins are depicted as being concentrated in the lamina (thick red lines) and also distributed throughout the nucleoplasm (thinner red lines). The filamentous nature of the lamins, especially in the nucleoplasm, remains hypothetical. Some of the known LEM domain proteins, including LAPs 2α and β, MAN1, otefin, and emerin are depicted. Also shown are other factors that are thought to interact directly or indirectly with the lamins, including YA, BAF, Rb, LBR, LAP 1, mGCL, and nesprin. The possible association between lamins and nuclear pore complexes, perhaps through NUP 153 is indicated. Two interphase chromosome domains are also shown. One contains a DNA replication center containing a higher concentration of nucleoplasmic lamins, RFC, PCNA, and DNA polymerase δ. For details, see text.

nuclear import. In addition, the lamins (except lamin C) have a CaaX motif, which undergoes cleavage of the last three amino acids and isoprenylation and methyl esterification of the terminal cysteine residue. Isoprenylation appears to be required for targeting the lamins to the inner surface of the nuclear envelope (Holtz et al. 1989; Kitten and Nigg 1991; Firmbach-Kraft and Stick 1993; Hofemeister et al. 2000). Interestingly, the carboxy-terminal 18 amino acids of lamin A, including the isoprenyl group, is removed by proteolysis (Weber et al. 1989).

The nuclear lamins, like their cytoskeletal counterparts, are largely resistant to extraction under conditions that solubilize the vast majority of cytoplasmic and nuclear proteins. For example, when cells are treated with high concentrations of non-ionic detergents in PBS, both the nuclear and cytoskeletal IF remain insoluble (Aebi et al. 1986; Goldman et al. 1986; Gerace and Burke 1988). The striking electron microscopic images of cells extracted in this way show that the nucleus retains its shape, and the lamina remains at the nuclear periphery (Capco and Penman 1983). These results have helped to define the lamina as the structure that is responsible for nuclear shape. The role of lamins in the mechanical stability of the nucleus has been confirmed by numerous experiments by use of gene knockouts or disruption of the lamin structure with lamin mutants (see below).

Despite the evidence that the lamins are required to maintain nuclear shape and mechanical integrity, little is known about their higher order structures in situ. In amphibian eggs, the nuclear lamina has been described as a network of 10-nm lamin filaments that immediately underlie the inner membrane of the nuclear envelope (Aebi et al. 1986; Goldberg and Allen 1996). In this case, the lamina is assembled primarily from one lamin isotype. In other cell types, the structure of the lamina has not been well defined, which may reflect a more complex composition of the lamina. For example, in mammalian cells, the lamina is composed of up to five lamin

isotypes (three A-types and two B-types) and there appears to be variability in the thickness of lamin B staining at the nuclear periphery within the same nucleus as seen by both light and electron microscopy (Belmont et al. 1993). The basis of this variability is not known, but it may reflect local variations in lamina structure and composition.

In addition to the peripheral lamina, there is substantial evidence that the lamins also form nucleoplasmic structures. These can appear as distinct foci or as a veil that fills the nucleoplasm as shown both by immunofluorescence and live-cell imaging using GFP-tagged lamins (Liu et al. 2000; Moir et al. 2000b). These structures are not pools of unincorporated lamins freely diffusing in the nucleus, as shown by fluorescence recovery after photobleaching (FRAP). In these experiments, fluorescence recovery rates in the nucleoplasm can be on the order of hours, implying that they represent relatively stable structures. Furthermore, immunoelectron microscopic evidence also suggests that lamins are present within the nucleoplasm (Hozak et al. 1995).

Studies of nuclear lamin assembly in vitro have revealed interesting differences relative to cytoskeletal IF. Purified cytoskeletal IF proteins readily self assemble into 10-nm filaments, either as homo- or heteropolymers (Parry and Steinert 1999). These appear morphologically identical to the IF structures seen in situ. In contrast, the final in vitro lamin assembly products are typically large paracrystalline arrays (Stuurman et al. 1998). The paracrystals do not exist in vivo under normal circumstances and appear to result from the lateral stacking of filamentous structures. The apparent difference between lamin assembly in vivo (as 10-nm filaments or other structures) and in vitro (paracrystals) suggests that lamin organization in vivo is regulated by interactions with other molecules.

The pathway of lamin assembly into paracrystals in vitro can be used to reveal the range of molecular interactions that may occur in vivo. For example, when samples from the earliest stages of lamin assembly are analyzed by electron microscopy, the lamins appear as long chains of molecules (Sasse et al. 1997, 1998). These chains are formed by head-to-tail interactions of lamin dimers, a structure that has not been observed during cytoplasmic IF assembly. This is supported by mutational analyses of the lamin rod domain, which show that the head-to-tail chains result from interactions between the rod amino terminus of one dimer with the rod carboxyl terminus of a second dimer, resulting in a very short region of overlap (Sasse et al. 1998). Furthermore, the head-to-tail interactions between dimers are abolished if the lamin protein is first phosphorylated in vitro with the mitotic kinase p34/cdc2 (Peter et al. 1990, 1991). This suggests a mechanism for the disassembly of lamin polymers when the nucleus breaks down during mitosis. The serine residues phosphorylated by p34/cdc2 are present in the amino- and carboxy-terminal non-α-helical domains of the lamins, further showing that these domains also have a role in regulating lamin assembly in vivo.

Assembly/disassembly of lamins during the cell cycle

As implied above, the nuclear lamins are rapidly disassembled during the prophase/metaphase transition in vertebrate cells. This disassembly is regulated by phosphorylation of the lamins by p34/cdc2 (Heald and McKeon 1990). After mitosis, the lamins are dephosphorylated and reassembled. This reassembly occurs at approximately the same time as nuclear envelope formation. However, the role of lamins in the initial stages of nuclear envelope assembly has been a contentious issue. For example, immunofluorescence observations have been contradictory with respect to the time that different envelope components associate with decondensing chromosomes. In some cases, lamins appear to assemble on chromosomes before they are surrounded by nuclear membranes, and in other cases, the lamins appear to assemble only after the nuclear membranes and pores are formed (Yang et al. 1997a; Chaudhary and Courvalin 1993). In live cells, determinations of the timing of the initial assembly of GFP-lamin B1 on chromosomes have been inconsistent. Some laboratories have reported that lamin B1 appears to bind and assemble on the periphery of chromosomes early in the process of envelope assembly (Moir et al. 2000b), whereas others report that lamin B1 assembles only after the envelope has formed (Daigle et al. 2001). Lamin A does not appear to assemble in the peripheral region of decondensing chromosomes, but accumulates in the nucleoplasm early after the envelope and pores have assembled (Dechat et al. 2000; Moir et al. 2000b). As G_1 progresses, lamin A is gradually incorporated into the lamina. These results suggest that A- and B-type lamins follow different pathways of assembly during cell division. The functional significance of these differences remains to be determined.

A role for lamins in nuclear envelope assembly

In animals, nuclear lamins appear to be involved in the assembly of the nuclear envelope. In vitro nuclear assembly systems prepared from a variety of cell types have been used in attempts to determine the role of lamins in the assembly of the nuclear envelope, including membranes and nuclear pore complexes (pores). In a number of experiments, lamins were immunodepleted from cell-free extracts prior to initiating nuclear assembly in vitro. The subsequent effects on nuclear envelope formation were monitored by use of a variety of membrane and pore markers. In some cases, immunoadsorption of lamins prevented chromosome decondensation, nuclear membrane formation, and nuclear pore assembly (Burke and Gerace 1986; Ulitzur and Gruenbaum 1989; Dabauvalle et al. 1991; Ulitzur et al. 1992, 1997). In other studies, depletion did not block nuclear envelope assembly (Newport et al. 1990; Meier et al. 1991), but the resulting nuclei were small, fragile, and lacked a lamina. These conflicting results can be explained if the immunodepletion protocols used in different laboratories result in differing amounts of residual lamin protein. In

some cases, this residual lamin may be adequate to initiate envelope assembly. Consistent with this hypothesis, immunoblots of nuclei assembled in lamin-depleted extracts were shown to contain some lamin (Jenkins et al. 1993). Therefore, only a small amount of lamin protein may be required for nuclear envelope formation (Lourim and Krohne 1993). However, it is clear from these studies that the assembly of a typical lamina is not required for the formation of nuclear membranes and pores.

Genetic experiments also support an important role for lamins in the assembly of nuclear membranes and pores. A mutation in *Drosophila* lamin Dm_0 reduces lamin expression, inhibits nuclear membrane assembly and induces the formation of annulate lamellae (cytoplasmic stacks of membrane containing nuclear pore-like structures; Lenz-Bohme et al. 1997). Another Dm_0 mutant has profound effects on nuclear morphology and *Drosophila* development (Guillemin et al. 2001). Similarly, an RNA interference block of lamin expression in *C. elegans* induced a large number of alterations including changes in nuclear shape, clustering of nuclear pores, and improper chromosome segregation during mitosis (Liu et al. 2000).

The role of lamins in nuclear membrane assembly has been examined directly by use of the carboxy-terminal non-α-helical domain of *Xenopus* lamin B3 (LB3T), which inhibits the in vitro assembly of lamin B3 into higher order structures (Lopez-Soler et al. 2001). When LB3T is added to *Xenopus* nuclear assembly extracts, a particular class of nuclear membrane vesicle (fusogenic) is blocked from associating with chromatin, resulting in the inhibition of the formation of the nuclear membrane as well the lamina and pores (Lopez-Soler et al. 2001). Interestingly, LB3 is normally associated with both fusogenic vesicles and chromatin during the early stages of nuclear assembly. The binding of LB3T to either of these components is sufficient to block nuclear membrane formation. These findings imply that under normal conditions, lamin–lamin interactions are involved in forming bridges that connect membrane vesicles to chromatin in the early stages of nuclear membrane assembly. These interactions may involve the head-to-tail assemblies observed during the initiation of lamin polymerization in vitro (Lopez-Soler et al. 2001). All of the information available to date indicates that although lamins are required for nuclear envelope assembly, a typical lamina is not. This suggests that different lamin structures may mediate different lamin-linked functions.

The regulation of the various lamin structures formed during normal nuclear envelope assembly may be determined by the association of lamins with other proteins. Metazoan cells express many proteins that have been reported to interact with the lamins (Cohen et al. 2001). These have been divided into two groups. The first group consists of integral proteins of the inner nuclear membrane. These include several isoforms of lamin associated protein 2 (LAP2), LAP1, emerin, MAN1, otefin, lamin B receptor (LBR), Nurim, nesprin, RING finger-binding protein (RFBP), A-kinase-anchoring protein 149 (AKAP149), p18 (an isoquinoline-binding protein which is also present in the ER), and probably UNC-84 (Goldberg et al. 1999; Cohen et al. 2001; Wilson et al. 2001; Zhang et al. 2001). The second group contains proteins that are not integral membrane components, but are concentrated mainly in the region of the nuclear lamina. These include germ cell-less (GCL), young arrest (YA), PP1 phosphatase, and the transcription factor Oct1 (Imai et al. 1997; Liu and Wolfner 1998; Steen et al. 2000; Cohen et al. 2001). In most cases, the roles of these lamin-associated proteins in nuclear assembly and other nuclear functions have not been determined. However, the addition of the constant domain of LAP2 isoforms to *Xenopus* extracts, prior to the initiation of nuclear assembly, produces structural abnormalities highlighted by discontinuous "scalloped" nuclear membranes surrounding chromatin (Gant et al. 1999). Even more dramatically, immunodepletion of LBR from a sea urchin nuclear assembly system blocks membrane binding to chromatin (Collas et al. 1996). It is obvious from these studies that the precise role of nuclear lamins in nuclear assembly will require an understanding of lamin interactions with other nuclear envelope proteins.

The organization of lamins in the interphase nucleus

During interphase, the nuclear lamins are continually synthesized and incorporated into the lamina (Gerace et al. 1984), suggesting that the lamins continue to polymerize within the nucleus throughout interphase. This is especially the case as cells progress from early to late G_1 when the nucleus grows very rapidly, indicating that lamins play a role in nuclear growth (Yang et al. 1997b). In addition, dominant negative lamin mutants lacking their amino terminus rapidly disrupt normal lamin organization (Spann et al. 1997; Moir et al. 2000a). Therefore, the structure of the lamina appears to be regulated by a subunit/polymer exchange mechanism.

Other evidence supporting the dynamic nature of the lamins during interphase has been derived from cells expressing GFP lamins (Broers et al. 1999; Moir et al. 2000b; Daigle et al. 2001). For example, FRAP studies show that during the initial stages of G_1, GFP-lamin B1 lamina fluorescence shows full recovery in 10 min (Moir et al. 2000b). Approximately 60 min after nuclei assemble, the half time ($t_{1/2}$) for full recovery exceeds 2 h. In cells transfected with GFP-lamin A, intense nucleoplasmic and lamina fluorescence is seen during the first 1–2 h of G_1. FRAP studies show that at these times the nucleoplasmic fluorescence recovers within seconds, and the lamina fluorescence recovers with a $t_{1/2}$ of ~90 min. This indicates that lamin A exists in two very different assembly states in the same cell.

Later in G_1, both GFP-lamin A and B patterns are seen to comprise a stable nucleoplasmic structure termed the "veil" in addition to the intensely fluorescent lamina. At other stages of interphase, FRAP rates greatly increase both in the veil and in the lamina regions (Moir et al. 2000b). In noncycling G_0 cells, there was little recovery of photobleached regions of the lamina containing GFP–

lamin B1 even after 45 h (Daigle et al. 2001). The FRAP results show that the nucleoplasmic lamins can also form a relatively stable structure (Fig. 2). However, these nucleoplasmic structures are much less resistant to detergent/high-salt extraction than the lamina. The biochemical and structural differences between these lamin structures may reflect the presence of distinct lamin substructures involved in mediating a variety of nuclear functions including nuclear envelope assembly (see above), DNA replication, transcription, and apoptosis (see below).

The involvement of lamins in DNA synthesis

DNA replication appears to require normal lamin organization. When nuclei are assembled in vitro in a lamin-depleted *Xenopus* interphase extract, the resulting nuclei do not replicate their DNA (Newport et al. 1990; Meier et al. 1991). Similar results are obtained upon the addition of the dominant negative lamin mutants that lack their amino-terminal domains, *Xenopus* ΔNLB3, or human ΔNLA (Ellis et al. 1997; Spann et al. 1997; Moir et al. 2000a). When these mutants are added to assembled nuclei, they disrupt the organization of nuclear lamins and block DNA synthesis (Ellis et al. 1997; Spann et al. 1997; Moir et al. 2000a). This correlation between normal lamin organization and DNA replication is also observed in vivo when DNA synthesis occurs unusually early in the cell cycle during the initial stages of *Xenopus* embryonic development. At these stages, lamins assemble during anaphase and subsequently replication begins in early telophase (Lemaitre et al. 1998). Furthermore, in human tumor cells during S-phase, cytoplasmic double minute chromosomes become enclosed by lamins before they replicate (Tanaka and Shimizu 2000).

In contrast, it has also been shown that an extract derived from highly concentrated isolated nuclei (termed the nucleoplasmic extract) can support the semiconservative replication of *Xenopus* genomic DNA in the absence of nuclear assembly and presumably lamins (Walter et al. 1998). To reconcile these disparate observations, it has been proposed that the major role of lamins in DNA synthesis is to support the nuclear envelope, allowing efficient transport and retention of replication factors. This could establish conditions necessary for achieving high concentrations of these factors (Walter et al. 1998). However, it should be pointed out that the nuclear membrane continues to act as a barrier to large molecules and that nuclear pores appear to function normally in nuclei in which lamin organization is disrupted and DNA synthesis is blocked (Spann et al. 1997; Moir et al. 2000a).

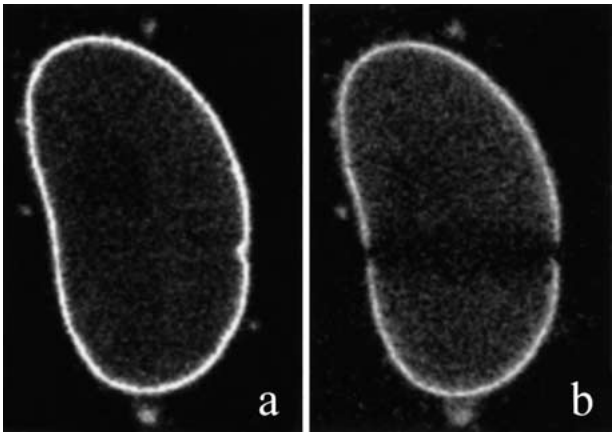

Figure 2. A living epidermal cell (PAM) expressing GFP-lamin A showing the presence of the lamina and the nucleoplasmic veil. A single optical section from the middle of the nucleus is shown before bleaching (*a*) and 60 min after the bleach zone was introduced (*b*). The bleach zone remains in both the peripheral nuclear lamina and the internal veil (Moir et al. 2000b).

Other studies suggest that lamins play a more direct role in DNA synthesis. During S phase, lamins colocalize with PCNA, a factor required for the elongation phase of replication, at sites of nucleotide incorporation (Moir et al. 1995). Consistent with this finding, PCNA is more easily extracted from nuclei assembled in lamin-depleted extracts (Jenkins et al. 1993). Furthermore, the normal localization(s) of both PCNA and RFC, another factor required for the elongation phase of DNA replication, are altered upon the addition of the mutant lamin, ΔNLB3 (Moir et al. 2000a). Both ΔNLB3 and ΔNLA appear to induce the redistribution of lamins, which leads to the formation of nucleoplasmic aggregates containing wild-type endogenous lamins, mutant lamins, RFC, and PCNA. This disruption does not, however, affect the distribution of ORC2, MCM3, or DNA polymerase α, three factors required for the initiation of DNA synthesis. Further support for a lamin function in the chain elongation phase of replication, and not the initiation phase, is derived from the finding that only short replication products are synthesized in lamin-disrupted nuclei. Upon reversal of the effects of the mutants, chain elongation is initiated rapidly as the nucleoplasmic aggregates disappear and the lamins reestablish their normal locations both within the lamina and the nucleoplasm (Spann et al. 1997; Moir et al. 2000a). Therefore, nuclear lamins may form a nucleoplasmic scaffold upon which the active elongation complexes required for DNA synthesis are assembled. However, other experiments have suggested that nuclear lamins may only be required to initially organize replication factors and once this occurs, lamins may no longer be required for DNA synthesis (Ellis et al. 1997). Resolving this question will require both the identification and characterization of additional factors that interact with nuclear lamins during DNA synthesis.

Nuclear lamins and transcription

The observation that regions of chromatin appear to be anchored to the lamina led to the suggestion that these sites might organize interphase chromatin and thereby regulate transcriptional activity (Moir et al. 1995). In support of this, it has been shown that alterations in lamin expression are correlated with changes in gene expression patterns. For example, lamin B3 is the major

lamin found in the early developmental stages of *Xenopus*, whereas lamin B1 expression is dramatically increased during the mid-blastula transition due to the unmasking of maternal RNA (Benavente et al. 1985; Stick and Hausen 1985). These increased levels of lamin B1 coincide with the induction of RNA polymerase II-dependent transcriptional activity. Similarly, in *Xenopus*, lamin B2 expression is induced during gastrulation, the time during which the three germ layers are established (Benavente et al. 1985; Stick and Hausen 1985). Furthermore, the induction of A-type lamins during development occurs during tissue differentiation in vertebrates (Rober et al. 1989). It has been proposed that expression of the A-type lamins may lock cells into a differentiated state by modifying chromatin organization (Peter and Nigg 1991). Consistent with this model, cancer cells that lose their differentiated phenotype express lower levels of lamin A (Venables et al. 2001). Attempts to obtain more direct evidence showing that the lamin composition of the nucleus affects transcription have produced mixed results. For example, the ectopic expression of lamin A in chick myogenic cells that normally express only lamin B induces the production of muscle-specific proteins (Lourim and Lin 1992). However, the ectopic expression of lamin A in an embryonic carcinoma cell line did not induce differentiation (Peter and Nigg 1991).

The specific function of lamins in transcription remains unknown. However, clues have been derived from a variety of different sources. Transcriptionally active genes and transcription factors have been identified in lamin-enriched nuclear matrix preparations. More specifically, Oct-1, a repressor of the collagenase gene, colocalizes in the nuclear periphery with lamin B (Imai et al. 1997). However, as cells approach senescence, the dissociation of Oct-1 from the nuclear periphery coincides with increased collagenase expression, suggesting that the repressor activity of this protein is related to its association with the nuclear lamina (Imai et al. 1997). Similarly, the *Drosophila* insulator element, *gypsy*, appears to localize close to the lamina, and this association may be important for its proper function (Gerasimova and Corces 1998). The finding that the retinoblastoma protein (Rb) interacts with A-type lamins in situ and in vitro further supports a role for lamins in transcription (Mancini et al. 1994; Ozaki et al. 1994). Rb represses the transcription of genes through its interactions with E2F (Kaelin 1999).

Further evidence for lamin involvement in transcription is provided by studies of the effects of the dominant negative lamin mutant, ΔNLA. When the lamin organization of animal cells is disrupted with this mutant, the synthesis of RNA polymerase II-dependent transcripts is dramatically inhibited (Spann et al. 2002). In contrast, the activities of RNA polymerases I and III do not appear to be affected. Interestingly, the disruption of lamin organization also alters the distribution of the TATA-binding protein, a component of the basal transcription factor TFIID, which is required for polymerase II activity. These results indicate that lamins may interact with the basal transcription machinery and provide a scaffold for the assembly or stabilization of active transcription complexes.

Lamin-associated proteins (LAPs) have also been implicated in transcription. For example, LAP2β interacts in vitro with the vertebrate GCL protein, which colocalizes with nuclear lamins in the lamina (Nili et al. 2001; Fig. 1). The GCL protein was originally described in *Drosophila* as a maternal nuclear envelope protein required for germ-cell formation (Jongens et al. 1994). The vertebrate GCL appears to interact with the DP3 subunit of the E2F–DP heterodimer, an S-phase transcription factor (de la Luna et al. 1999). Furthermore, overexpression of LAP2β, mouse GCL, or both, reduces transcriptional activity regulated by the E2F–DP complex (de la Luna et al. 1999; Nili et al. 2001).

Nuclear lamins and their associated proteins interact with chromatin

The proposed roles for lamins in replication and transcription may also be related to the interactions of lamins and lamin-associated proteins with chromatin. Early evidence suggesting a lamin–chromatin interaction came from direct observations of nuclei in a wide variety of species by use of microscopic methods. For example, peripheral heterochromatin is closely associated with the lamina in the nuclei of cells in a wide range of vertebrate and invertebrate species (Fawcett 1966; Dessev and Goldman 1988; Paddy et al. 1990; Fig. 3). In vitro, it has been shown that lamins can bind directly to chromatin (Taniura et al. 1995). There is also evidence that lamins can bind DNA sequences known as matrix-attachment regions (MARs) and scaffold-attachment regions (SARs) (Luderus et al. 1992, 1994; Zhao et al. 1996).

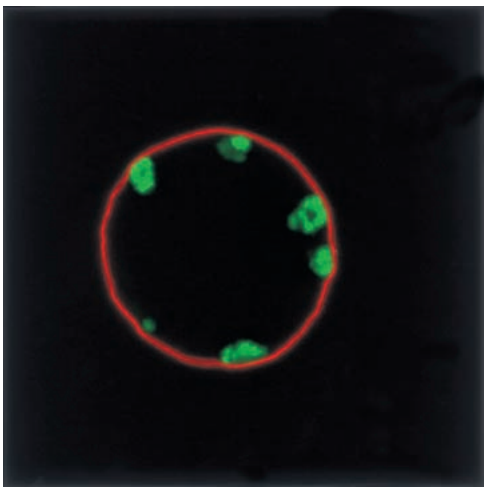

Figure 3. The isolated late prophase premeiosis I nucleus of the egg of the surf clam, *Spisula solidissima* (Dessev et al. 1989). This nucleus has been double labeled with an antibody directed against the clam lamin (red) and a human autoantibody that reacts with chromatin (green). Note the close association between the condensed chromosomes and the lamina (kindly provided by Anne Goldman, North-Chicago, Western University Medical School, IL).

Two of the isoforms of LAP2, LAP2α and LAP2β, also bind to chromatin. Stable binding of these LAPs requires both a chromatin-binding domain and the LEM domain, a conserved region of ~43 amino acids also found in emerin, MAN1, and otefin (Dechat et al. 2000; Lin et al. 2000). Furthermore, *Xenopus* LAP2 isoforms can bind to DNA directly in vitro (Shumaker et al. 2001). Biochemical and biophysical studies show that LAP2 isoforms also bind to a DNA-binding protein, BAF, at their LEM domains (Furukawa 1999; Cai et al. 2001; Shumaker et al. 2001). BAF was first identified as an inhibitor of retroviral DNA autointegration (Lee and Craigie 1998). These results suggest that lamins can interact with chromatin via their connections to LAPs. For example, lamins could bind to LAP2 isoforms and, in turn, these could readily bind to BAF, thereby forming links between lamins and chromatin (see Fig. 1). Recently, emerin has been shown to bind directly to BAF in vitro leading to the proposal that BAF also binds to the other LEM domain proteins (Lee et al. 2001; Wilson et al. 2001). Therefore, there are many possible combinations of lamin /LEM domain protein/BAF interactions that may influence chromatin structure and specific nuclear processes such as replication and transcription (Cai et al. 2001; Laguri et al. 2001; Wolff et al. 2001).

One such combination that may play a role in changing patterns of gene expression is based on biochemical evidence showing that emerin binds to lamin A (Clements et al. 2000; Sakaki et al. 2001). Therefore, the expression of lamin A during cell differentiation may induce chromatin reorganization and alter gene expression through its interactions with emerin/BAF/DNA complexes. A BLAST search for LEM domain proteins shows that this domain is found in three *C. elegans* proteins (Lee et al. 2000), at least six *Drosophila* proteins, and in many human proteins (Y. Gruenbaum, unpubl.). It will be of great interest to determine whether any of these proteins represent additional lamin-binding partners. Taken together, the chromatin-binding properties of the lamins and the LEM-domain proteins are consistent with a model in which the nuclear lamins influence chromatin organization and, therefore, gene activity (Fig. 1).

It is possible that there are other nuclear envelope proteins that interact with the lamins. In *Drosophila*, YA (young arrest; see Fig. 1) protein is a maternally derived nuclear lamina component that is essential for the transition from meiosis to mitosis during the initiation of embryogenesis (Goldberg et al. 1998; Yu et al. 1999). Nuclear entry of YA correlates with developmentally regulated changes in its phosphorylation state. Another potential group of lamin-binding proteins includes those containing the SUN domain, a conserved region of between 113 and 178 amino acids found in Sad1, UNC-84, and two human genes. Both Sad1 and UNC-84 are located in the nuclear envelope/lamina (Malone et al. 1999).

Lamins and apoptosis

Apoptosis is characterized by a dramatic reduction in nuclear size and chromatin condensation. Chromatin condensation is usually, but not always, accompanied by chromatin fragmentation. Ultimately, the nucleus fragments into small bodies containing highly condensed chromatin. The alteration of nuclear lamin organization appears to be a key step in the initiation and execution phases of apoptotic cell death. Interestingly, the state of lamin assembly may also be involved in triggering apoptosis, as inhibition of the assembly of lamin B induces cell death (Steen and Collas 2001).

During apoptosis, lamins are cleaved by caspases (Lazebnik et al. 1995; Takahashi et al. 1996). The nuclear lamins were one of the first proteins identified as caspase targets and the cleavage of the lamins is frequently used as a marker for caspase activation and the induction of apoptosis. The single caspase cleavage site of lamin A was mapped to aspartic acid 230 (Takahashi et al. 1996). This residue lies in the 2B region of the central rod domain, which is one of the most highly conserved regions in all known intermediate filament proteins. This domain is critical for polymerization of IF proteins into higher order structures. Most, but not all, cytoplasmic IF are also cleaved at this caspase recognition site. In the case of human lamins A and B1, the aspartic acid that is cleaved is conserved, but the remainder of the caspase recognition sequence differs, suggesting that different caspases may be involved in the cleavage of different lamin isotypes (Takahashi et al. 1996, 1997; Slee et al. 2001).

The cleavage of lamins by caspases probably serves to disassemble the lamina during apoptosis and this disassembly may be essential for nuclear apoptosis to be completed successfully. This is based on experiments in which a caspase-uncleavable mutant was expressed in HeLa cells undergoing apoptosis (Rao et al. 1996). The presence of the mutant lamin slowed the progression of apoptosis, including nuclear shrinkage and chromatin condensation. On the basis of the information available on the functions of the lamins in DNA replication and in transcription (see above), lamin degradation appears to play a critical role in shutting down vital nuclear processes during apoptosis.

Local disassembly of the lamina during viral transport and infectivity

The nuclear envelope represents a barrier for both DNA and RNA viruses that replicate and/or assemble in the nucleus. It is known that DNA viruses, such as herpesvirus, replicate and assemble nucleocapsids in the cell nucleus and exit by budding through the inner nuclear membrane. In many cells, this nucleocapsid egress is accompanied by the disassembly of lamins at the nuclear periphery during the late stages of infection (Osterrieder et al. 1998; Scott and O'Hare 2001). Interestingly, the herpesvirus IR6 protein colocalizes with nuclear lamins in the nucleoplasm, and coimmunoprecipitates with the lamins, suggesting a direct interaction (Osterrieder et al. 1998). Viral strains with mutations in the IR6 protein are less infectious and the IR6 protein does not colocalize with the lamins. Therefore, these results suggest that

viral protein interaction with lamins is required for the disassembly of the lamina during the movement of the herpesvirus from the nucleus to the cytoplasm.

In the case of the RNA virus, HIV-1, the preintegration complex (PIC) is a large nucleoprotein complex that must enter the nucleus so that viral DNA can be integrated into the host genome (Sherman et al. 2001). Importin α interacts with NLS signals on HIV proteins, indicating that nuclear pore transport may be involved in this process (Sherman et al. 2001). However, the PIC is larger than the presumed channel size of the pore and the mechanism of PIC transport into the nucleus is therefore not clear. Recently, it was shown that the expression of the single viral protein Vpr induces herniations or blebs in the nuclear envelope (de Noronha et al. 2001). Cells transfected with the Vpr protein arrest in G_2, allowing for extended periods of viral transcription. Vpr mutants that do not arrest the cell cycle do not induce these herniations. The nuclear lamina is locally disassembled as indicated by alterations in lamin structure at the site of these herniations and nuclear pore complexes are absent in these regions. The resulting blebs frequently burst, allowing cytoplasmic constituents to enter the nucleus. Remarkably, these local openings in the nuclear envelope reseal over short time periods. Similar nuclear abnormalities are also observed in cells infected with the complete HIV-1 virus. These transient openings in the nuclear envelope suggest a mechanism for PIC entry into the nucleus, supporting a direct link between the viral life cycle and structural changes in the nuclear lamins comprising the lamina (de Norohna et al. 2001).

Understanding lamin functions using model genetic systems

In *Drosophila* there are two lamin genes, a B-type (Dm_0) and an A/C type (*lamin C*). When a P element is inserted into the first intron of the *Drosophila* lamin Dm_0 gene (lam^P), there is a reduction in the expression of lamins (Lenz-Bohme et al. 1997). Homozygous flies exhibit delayed developmental progression, are unable to fly, and are sterile. The mutant flies lack a normal lamina. In addition, in these flies, many cells have incomplete nuclear envelopes and abnormal clusters of nuclear pore complexes (Lenz-Bohme et al. 1997). Another P-element disruption of Dm_0 causes defects in tracheal branch migration, whereas germ-line mutants produce phenotypes from slight to strong dorsalization, reminiscent of fs(1)K10 or *squid* (Guillemin et al. 2001). The dorsalization could be due to the mislocalization of Gurken mRNA and protein, a factor controlling dorsal-ventral polarity. The authors of this study suggest that lamins may be required for either the localization of Gurken in the cytoplasm or the expression of genes involved in this localization (Guillemin et al. 2001).

C. elegans has a single lamin gene, *lmn-1*. When the gene product of *lmn-1* (Ce-lamin) is removed by RNA interference (RNAi), embryos stop growing after several hundred nuclei are formed (Liu et al. 2000). This indicates that Ce-lamin is essential. However, some RNAi embryos have significant nuclear alterations during the first few nuclear divisions. This is exemplified by the formation of abnormal chromosome bridges, unequal distribution of chromatin to daughter cells, and abnormal chromosome condensation. The nuclei were also misshapen and very plastic as shown by substantial shape changes over short time intervals. In addition, nuclear pore complexes were clustered (Liu et al. 2000). Importantly, *C. elegans* is a model system with only one lamin gene and in which most lamin protein can be removed. Therefore, lamin functions can be studied by the addition of lamin mutants.

Laminopathies: an emerging class of human diseases

To further identify the roles of lamins A and C, the *LMNA* gene has been knocked out in mice (Sullivan et al. 1999). These mice appear normal at birth, but within 2–3 wk their growth rate slows significantly. After 3–4 wk, the null mice exhibit an abnormal gait characterized by a stiff walking posture leading to death by week 8. Histological examinations show that the mice have skeletal and cardiac muscle wasting and a loss of white fat. Cultured fibroblasts from lamin A –/–; mice exhibit abnormal nuclear blebs with significantly reduced amounts of lamins, LAP2, and the nuclear pore component NUP153. Ultrastructural studies of these cells show that condensed heterochromatin is not adjacent to the nuclear membrane in the blebbed regions (Sullivan et al. 1999). The distribution of emerin (see Fig. 1) is also altered in these cells as shown by its location in the ER in addition to the nuclear periphery. Reintroducing lamin A into these cells restores normal emerin localization to the inner nuclear membrane (Sullivan et al. 1999). A similar relationship between A-type lamin expression and emerin localization is also observed when human HL-60 leukemia cells are induced to differentiate into granulocytes with retinoic acid. Under these conditions, there is a loss of lamins A/C, and emerin is found in the cytoplasm. When these cells are treated with phorbol ester (TPA) to induce differentiation into macrophages, lamins A/C are expressed and emerin localizes to the nuclear envelope (Olins et al. 2001).

One of the most interesting features of the knockout mice is the similarity of their symptoms to those of patients with Emery Dreifuss Muscular Dystrophy (EDMD) (Emery and Dreifuss 1966). Recently, mutations in *LMNA* have been identified as causative for the autosomal dominant form of EDMD (Bonne et al. 1999). Autosomal recessive mutations in *LMNA* have also been identified (Raffaele di Barletta et al. 2000). Historically, the first genetic locus linked to EDMD was *emerin.* Mutations in this gene cause an X-linked recessive form of this disease (Bione et al. 1994). It was only later that emerin was identified as an inner nuclear membrane protein (Manilal et al. 1996). Typically, EDMD symptoms are first detected at 4–5 years of age and the disease progresses slowly. Patients exhibit tendon contractures in the heels, elbows, and neck, wasting and weakness of the musculature of the pelvic girdle, biceps, and triceps,

the disappearance of deep tendon reflexes, cardiac conduction problems, and facial muscle weakness. Other mutations in *LMNA* cause dilated cardiomyopathy (DCM) (Fatkin et al. 1999), familial partial lipodystrophy (FPLD) (Cao and Hegele 2000; Shackleton et al. 2000), and limb girdle muscular dystrophy (LGMD) (Muchir et al. 2000). FPLD is not evident until puberty, at which time there is a loss of subcutaneous fat in regions such as the extremities and gluteal areas along with excess fat deposition in the neck, back, and face, as well as insulin resistance and diabetes (Kobberling and Dunnigan 1986). LGMD is characterized initially by pelvic girdle weakness and later by weakness of the humeral muscles (van der Kooi et al. 1996).

To date, there are about 50 known mutations in *LMNA* that cause laminopathies (Fig. 4; Table 1). These include point mutations, frameshift mutations, deletions, and two nonsense mutations. Interestingly, mutations for EDMD are present in all domains of *LMNA*, whereas DCM and LGMD mutations are only present in the rod and carboxy-terminal domains. Furthermore, FPLD mutations have only been found in the non α-helical tail domain of A-type lamins (Fig. 4). Diseases caused by *LMNA* mutations have been found in all exons except for 10 and 12. The lack of mutations in exon 10 is interesting because there is a naturally occurring lamin without exon 10 (lamin AΔ10; Machiels et al. 1996). Therefore, it is possible that mutations in exon 10 are not debilitating under normal circumstances.

Surprisingly, the clinical expression of the same *LMNA* mutation often varies in severity among members of the same family (Fatkin et al. 1999; Cao and Hegele 2000; Hegele et al. 2000; Brown et al. 2001). Furthermore, the clinical designations of laminopathies are known to overlap, and patients with the most severe forms of EDMD frequently have symptoms of the other lamin-linked diseases. The differences in the genetic backgrounds of individual family members may explain these observations, as allelic variation in lamin binding or regulatory proteins could alter the effect of a particular lamin mutation. The findings that mutations of both A-type lamins and emerin result in the same clinical symptoms also support this possibility. Consequently, EDMD, FPLD, DCM, and LGMD may represent different degrees of penetrance of the same disease.

It is obvious that the nuclear lamins are involved in a number of critical processes including nuclear assembly, apoptosis, DNA synthesis, and possibly transcription. Interestingly, the lamins assemble a number of different structures during the cell cycle. Some of these structures may be acting as specialized scaffolds to facilitate the proper organization of factors required for particular nuclear functions. Consistent with this role, the loss of lamins has been shown to be lethal in mice, *Drosophila*, and *C. elegans*. Further insights into lamin functions are coming from the analyses of human diseases involving mutations of A-type lamins. Interestingly, the human laminopathies in which *LMNA* is mutated appear to affect only a few tissues, such as muscle and fat. These diseases develop slowly with symptoms typically appearing in adults, as opposed to the lamin A knockout mice, which die within 2 mo of birth. These observations suggest that the lamin mutations detected in patients do not completely block the functions of A-type lamins.

The mechanism by which a mutation in *LMNA* alters nuclear function and causes disease remains unclear. It is possible that mutant lamin A weakens the lamin polymer, resulting in fragile nuclei. For muscles and tendons, the stress from muscle contraction might deform or rup-

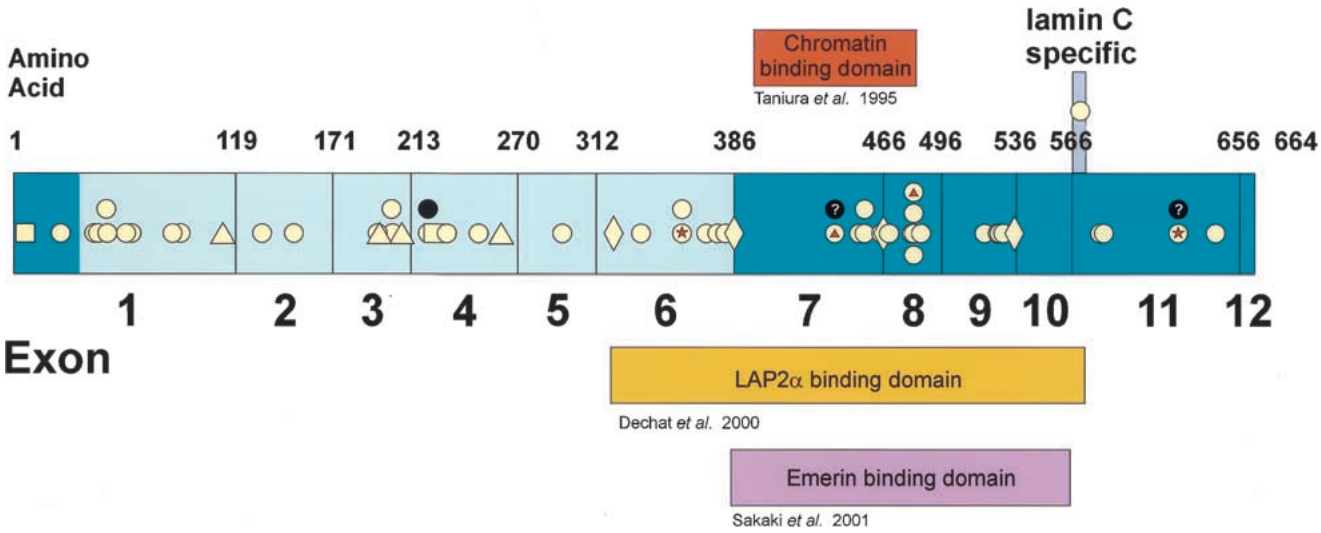

Figure 4. Mutations in lamin A that are known to cause human disease. The dark blue regions show the non-α-helical domains and the light blue shows the rod domain. Also indicated are the proposed chromatin, LAP and emerin-binding domains. The known protein mutations are indicated by squares, circles, triangles, and diamonds to indicate nonsense, point, deletion, and frameshift mutations, respectively. The red stars or the red triangles indicate double mutations. The black circle indicates a recessive mutation. (?) Synergistic mutations that may also be recessive. The specific amino acid modifications are shown in Table 1.

Table 1. *Lamin A mutations indicated in Figure 4 that cause disease*

Mutation[a]	Clincal phenotype[b]	Reference	Mutation	Clinical phenotype	Reference	Mutation	Clinical phenotype	Reference
Q6X	EDMD	(Bonne et al. 1999)	H222P	EDMD	(Bonne et al. 2000)	N456K	EDMD	(Bonne et al. 2000)
R25P	EDMD	(Brown et al. 2001)	H222Y-Recessive	EDMD	(Raffaele di Barletta et al. 2000)	G465D	FPLD	(Speckman et al. 2000)
A43T	EDMD	(Brown et al. 2001)	R225X	DCM	(Jakobs et al. 2001)	466 FS	DCM	(Genschel et al. 2000)
Y45C	EDMD	(Bonne et al. 2000)	G232E	EDMD	(Bonne et al. 2000)	I469T	EDMD	(Raffaele di Barletta et al. 2000)
R50P	EDMD	(Bonne et al. 2000)	R249Q	EDMD	(Raffaele de Barletta et al. 2000)	Y481H	LGMD	(Kitaguchi et al. 2001)
R50S	EDMD	(Brown et al. 2001)	ΔK261	EDMD	(Felice et al. 2000)	R482W	FPLD	(Shackleton et al. 2000)
R60G	DCM	(Fatkin et al. 1999)	Q294P	EDMD	(Bonne et al. 2000)	R482L	FPLD	(Shackleton et al. 2000)
I63S	EDMD	(Bonne et al. 2000)	321 FS	DCM	(Brodsky et al. 2000)	R482Q	FPLD	(Shackleton et al. 2000)
L85R	DCM	(Fatkin et al. 1999)	R336Q	EDMD	(Raffaele di Barletta et al. 2000)	K486N	FPLD	(Shackleton et al. 2000)
R89C	EDMD	(Sewry et al. 2001)	E358K/ R624H	EDMD	(Brown et al. 2001)	W520S	EDMD	(Bonne et al. 2000)
ΔE112	EDMD	(Bonne et al. 2000)	E358K	EDMD	(Bonne et al. 2000)	R527P	EDMD	(Bonne et al. 1999)
R133P	EDMD	(Brown et al. 2001)	M371K	EDMD	(Bonne et al. 2000)	T528K	EDMD	(Bonne et al. 2000)
T150P	EDMD	(Felice et al. 2000)	R377H	LGMD	(Muchir et al. 2000)	L530P	EDMD	(Bonne et al. 1999)
N195K	DCM	(Fatkin et al. 1999)	G381A	EDMD	(Sewry et al. 2001)	536 FS	LGMD	(Muchir et al. 2000)
R196S + ΔLQT 197–199	EDMD	(Brown et al. 2001)	R386K ± FS	EDMD	(Bonne et al. 2000)	R571S	DCM	(Fatkin et al. 1999)
E203G	DCM	(Fatkin et al. 1999)	V440M (Recessive)[c]	(FPLD)	(Hegele et al. 2000)	R582H	FPLD	(Speckman et al. 2000)
E203K	DCM	(Jakobs et al. 2001)	V440M/ R482Q	FPLD	(Hegele et al. 2000)	R584H	FPLD	(Vigouroux et al. 2000)
ΔK208	LGMD	(Muchir et al. 2000)	R453W	EDMD	(Bonne et al. 1999)	R624H (Recessive)[c]	(EDMD)	(Brown et al. 2001)
			N456I	EDMD	(Brown et al. 2001)	R644C	DCM	(Genschel et al. 2001)

[a]The amino acid changes are shown. If different DNA base pair changes cause the same mutation, the amino acid mutation is listed only once.
[b]The phenotypes are as follows: (EDMD) Emery Dreifuss Muscular Dystrophy; (DCM) dilated cardiomyopathy; (LGMD) limb girdle muscular dystrophy; (FPLD) familal partial lipodystropy.
[c]These mutations cause very severe phenotypes when paired with a second mutation, but have not been shown to have a mutant phenotype.

ture these fragile nuclei, resulting in cell death and muscle wasting by inducing apoptosis (Sullivan et al. 1999). Alternatively, the deformation of a fragile nucleus might disrupt the interactions of lamins and their binding partners linking them to chromatin (see Fig. 1), which could affect processes such as replication and transcription, both of which appear to involve lamins. On the other hand, these explanations do not appear to account for the mutations in *LMNA* that alter fat deposition. It is possible that laminopathies therefore arise, not due to nuclear fragility, but rather to an alteration in the affinity of lamin A for a cell type-specific binding partner. Consistent with this hypothesis, muscle cells and adipocytes both arise from mesenchymal stem cells (Prockop 1997), and as such, they may share unique lamin associated protein(s) (Wilson 2000). Alternatively, mutations in lamin A might also block the formation of specialized lamin structures (scaffolds) and thereby block interactions with particular binding partners. In either case, lamin A mutations could result in the inhibition of a critical nuclear function in a particular cell type.

Direct analyses of the effects of the mutations of *LMNA* identified in human diseases have recently been

undertaken. The examination of fibroblasts obtained from a number of FPLD patients indicate that the mutations in *LMNA* result in an increased fragility and disorganization of the nuclear envelope (Vigouroux et al. 2001). In a similar vein, lamin A mutants linked to human diseases have been expressed in cells possessing normal A-type lamins and in cells isolated from mice that lack A-type lamins (Östlund et al. 2001; Raharjo et al. 2001). These studies indicate that the disease linked *LMNA* mutations also alter the organization of the components of the nuclear envelope. Further characterization of the effects of these mutations may permit the identification of the domains of lamins and specific lamin-binding partners that are involved in particular nuclear functions such as replication and transcription.

In closing, studies of the nuclear lamins have advanced significantly over the past two decades. The early view of the lamins as a static nuclear exoskeleton, a bystander to nuclear function, is giving way to the view that nuclear lamins form dynamic polymers that comprise a variety of structures intimately involved in nuclear processes such as replication and transcription. Finally, we believe that ongoing studies of lamin function will help to determine the role that structural organization plays in the regulation of the many processes that take place within the nucleus.

Acknowledgments

We thank the National Cancer Institute (no. CA31760 to R.G.), the Gruss Lipper Foundation Fellowship (Y.G.), and the Marine Biological Laboratory for grant support, and Laura Davis for help in preparing the manuscript.

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Robert D. Goldman, Yosef Gruenbaum, Robert D. Moir, et al.

Genes Dev. 2002, **16:**
Access the most recent version at doi:10.1101/gad.960502