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Nuclear Envelope, Nuclear Lamina and Inherited Disease

Howard J. Worman¹ and Jean-Claude Courvalin²

¹Departments of Medicine and of Anatomy and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, NY 10032 USA

²Departement de Biologie Cellulaire, Institut Jacques Monod, CNRS, Universites Paris 6 and 7, 75251 Paris cedex 05 France

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Correspondence:

Howard J. Worman
Department of Medicine
College of Physicians and Surgeons
Columbia University
630 West 168th Street
10th Floor, Room 508
New York, NY 10032
Telephone: (212) 305-8156
Fax: (212) 305-6443
Email: hjw14@columbia.edu

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Abstract

The nuclear envelope is composed on the nuclear membranes, nuclear lamina and nuclear pore complexes. In recent years, mutations in nuclear envelope proteins have been shown to cause a surprisingly wide array of inherited diseases. While the mutant proteins are generally expressed in most or all differentiated somatic cells, many mutations cause fairly tissue-specific disorders. Perhaps the most dramatic case in mutations in A-type lamins, intermediate filament proteins associated with the inner nuclear membrane. Different mutations in the same lamin proteins have been shown to cause striated muscle diseases, partial lipodystrophy syndromes, a peripheral neuropathy and disorders with features of severe premature aging. In this review, we summarize fundamental aspects of nuclear envelope structure and function, the inherited diseases caused by mutations in lamins and other nuclear envelope proteins and possible pathogenic mechanisms.

Key Words: Nuclear envelope, lamin, muscular dystrophy, cardiomyopathy, lipodystrophy, peripheral neuropathy, aging, progeria

I. Introduction

The nuclear envelope separates the cytoplasm from the nucleus in eukaryotic cells. It is composed of the nuclear membranes, nuclear lamina and nuclear pore complexes. It has become a focus of increasing attention over the past decade, initially because of the identification of all the components of the nuclear pore complexes and the elucidation of mechanistic details of nucleocytoplasmic transport. More recently, research on the nuclear envelope has been headed in new directions due to the discoveries that mutations in several of its protein components cause a wide range of inherited diseases. This has resulted in attempts to associate what is known, and even what is not known, about nuclear envelope function with disease phenotypes. We summarize here what is known about nuclear envelope structure and function, the inherited diseases caused by mutations in lamins and other nuclear envelope proteins and possible pathogenic mechanisms.

II. Nuclear Envelope Structure, Function and Proteins

The nuclear envelope is composed of the nuclear membranes, nuclear pore complexes and nuclear lamina (Figure 1). The nuclear membranes are divided into three morphologically distinct but interconnected domains: outer, inner and pore. The pore membranes connect the inner and outer nuclear membranes at numerous points and are associated with the nuclear pore complexes. Pore membranes contain unique integral proteins, such as gp210 and POM121 in mammals and POM152 in yeast, which form parts of the nuclear pore complexes (Wozniak *et al.*, 1989,1994; Hallberg *et al.*, 1993). Nuclear pore complexes are composed of multiple copies of approximately 30 to 50 different proteins (Rout *et al.*, 2000; Cronshaw *et al.*, 2002). The structure of the pore complex, its protein composition and its role in nucleocytoplasmic transport has been the topic of several relatively recent reviews (Bednenko *et al.*, 2003; Fahrenkrog and Aebi, 2003; Suntharalingam and Wenthe, 2003; Cronshaw and Matunis, 2004; Rabut *et al.*, 2004).

A. Outer Nuclear Membrane and Perinuclear Space

The outer nuclear membrane contains ribosomes on its outer surface and has long been assumed to be identical in protein composition to the rough endoplasmic reticulum membrane, with which it is directly continuous. However, recent data suggest that the outer nuclear membrane contains integral proteins involved in nuclear positioning that are not localized to the bulk endoplasmic reticulum (Starr and Han, 2003). Among outer nuclear membrane proteins involved in nuclear positioning are the products of two genes, nesprin 1 and 2, that encode polypeptides containing spectrin repeat sequences (Zhang *et al.*, 2001, 2005; Young and Kothary, 2005). Spectrin repeats were first identified in large structural proteins, the best characterized being plasma membrane or cytoplasmic proteins as dystrophin and alpha-actinin. The general structure of spectrin repeat-containing proteins is a central domain containing the repeats that are competent for self-association, an amino-terminal actin-binding region composed of two calponin

homology domains and a carboxyl-terminal region containing a distinct functional domain. The carboxyl-terminal regions function in activities such as a membrane association, intermediate filament binding and microtubule binding. Nesprins have this general structure with a transmembrane segment in their carboxyl-terminal regions. Alternative transcription initiation and RNA splicing generate multiple nesprin isoforms with molecular masses ranging from approximately 50 kDa (nesprin-alpha2) to 800 kDa (nuance). These proteins can laterally diffuse in the endoplasmic reticulum membrane, but while the smaller isoforms are able to reach the inner nuclear membrane, the larger isoforms are excluded from this membrane, likely due to the restricted size of the lateral channels of the nuclear pore complex (Soullam and Worman, 1995). However, the larger nesprin isoforms are enriched in the outer nuclear membrane by interactions of their luminal carboxyl-terminal domains with perinuclear luminal SUN domains of integral inner nuclear membrane proteins such as UNC84 and Matefin in *Caenorhabditis elegans* and SUN1 and SUN2 in mammals (Malone *et al.*, 1999; Lee *et al.*, 2002; Hodzic *et al.*, 2004; Fridkin *et al.*, 2004) (Figure 1). An example is the spectrin repeat-containing protein ANC-1 in *Caenorhabditis elegans*, which contains a perinuclear domain that interacts directly or indirectly with the perinuclear SUN domain of UNC84 (Starr and Han, 2002).

In the cytoplasm, different nesprin isoforms are associated via their carboxyl-terminal transmembrane segments not only with the nucleus but also with other organelles, in particular the endoplasmic reticulum and mitochondria, and through their amino-terminal domains with the actin cytoskeleton. These interactions are of importance during cellular differentiation, for example during myogenesis when myoblasts fuse into highly organized multinucleated muscle fibers in which precise spatial organization is a prerequisite for function (Zhang *et al.*, 2005). Outer nuclear membrane connections to microtubules are also of physiological importance. ZYG-12 in *Caenorhabditis elegans* is retained in the outer nuclear membrane by binding to SUN1 in the perinuclear space and to the cytoskeleton by binding dynein and microtubules via its amino-terminal domain (Malone *et al.*, 2003). As a result, ZYG-12 maintains the stable attachment of the centrosome to the nucleus, which is necessary for positioning the nucleus in the cell and pulling the nuclear membrane during prometaphase (Beaudouin *et al.*, 2002; Salina *et al.*, 2002). Similar nuclear membrane and dynein-microtubule-centrosome connections occur with Klarsicht proteins in *Drosophila* photoreceptor nuclei (Patterson *et al.*, 2004), where both these proteins and nuclear lamins are required for nuclear migration in the developing eye. The SUN binding domain of Klarsicht and related proteins has been named the KASH (Klarsicht, Anc-1, Syne-1, homology) domain (Figure 1).

Similar to the outer nuclear membrane, the perinuclear space between the inner and outer nuclear membranes has been considered identical to the continuous endoplasmic reticulum lumen. One could imagine, however, that the composition of the perinuclear space could differ from the bulk endoplasmic reticulum lumen as portions of integral proteins localized to the inner and pore membranes within this luminal region could bind to resident non-membrane proteins (Figure 1). Recent data indeed demonstrate that torsinA, a luminal endoplasmic reticulum protein mutated in DYT1 dystonia (see below),

concentrates in the perinuclear space by binding to the luminal domain of lamina-associated polypeptide 1 when mutated (Goodchild and Dauer, 2005). Hence, the outer nuclear membrane and perinuclear space appear to be differentiated subdomains of the rough endoplasmic reticulum membrane and lumen.

B. Nuclear Lamina

Using electron microscopy, Fawcett (1966) first described the nuclear lamina of vertebrate cells as a fibrous structure underlying the inner nuclear membrane. Approximately a decade later, Blobel and colleagues (Aaronson and Blobel, 1975; Dwyer and Blobel, 1976; Gerace *et al.*, 1978) demonstrated that the interphase vertebrate lamina is associated with nuclear pore complexes and composed of three major polypeptides called lamin A, lamin B and lamin C. At around the same time, Franke and colleagues (Scheer *et al.*, 1976) obtained biochemical and morphological evidence that a network of fibrils connects the nuclear pore complexes in amphibian oocytes. Gerace and Blobel (1980) first showed that depolymerization of the nuclear lamina during mitosis in cycling cells correlated with hyperphosphorylation of its major protein components. A decade later, specific mitotic phosphorylation sites associated with lamina disassembly were identified (Heald and McKeon, 1990; Ward and Kirschner, 1990; Peter *et al.*, 1990). In 1986, Aebi *et al.* (1986) and Goldman *et al.* (1986) provided morphological and biochemical evidence that the nuclear lamina was an intermediate filament-like structure. That same year, cDNA cloning in the laboratories of Blobel (Fisher *et al.*, 1986) and Kirschner (McKeon *et al.*, 1986) showed that nuclear lamins were members of the intermediate filament protein family.

Like their cytoplasmic intermediate filament counterparts, lamins contain head and tail domains of variable structure and conserved alpha-helical central rod domains. Members of the intermediate filament protein family polymerize to form filaments approximately 10 nm in diameter (Herrmann and Aebi, 2004). The basic building block is the coiled-coiled dimer, which polymerizes to form the higher ordered macromolecular structures. Although all of the different mammalian lamin proteins interact in the yeast two-hybrid assay and *in vitro* (Ye and Worman, 1995; Schirmer and Gerace, 2004), it is not clear whether heteropolymers or only homopolymers of lamins form filaments *in vivo* and, if so, at what stoichiometries. It is also unclear if lamins in mammalian somatic cell nuclei polymerize between the inner nuclear membrane and chromatin by the same mechanism as intermediate filament proteins polymerize in the cytoplasm to form 10 nm diameter filaments.

In contrast to vertebrate cytoplasmic intermediate filament proteins, nuclear lamins contain an additional 42 amino acids in their rod domains. They also have nuclear localization signals in their tail domains. Except for lamin C, lamins contain CAAX boxes and are prenylated, specifically farnesylated, either permanently or transiently at their carboxyl termini (Beck *et al.*, 1988,1990; Wolda and Glomset, 1988; Farnsworth *et al.*, 1989; Weber *et al.*, 1989; Sinensky *et al.*, 1994) (Figure 2). The terminal three amino acids of the CAAX box are cleaved by a protease during the prenylation process (Figure 2). Lamin A is synthesized as a precursor, prelamin A, which is farnesylated and then proteolytically processed twice, resulting in the removal of 18 carboxyl-terminal

amino acids (Sinensky *et al.*, 1994) (Figure 2). Lamins also contain an S-type immunoglobulin fold in their tail domains (Dhe-Paganon *et al.*, 2002; Krimm *et al.*, 2002).

Lamins have been identified in numerous eukaryotic species, including the model invertebrate organisms *Drosophila melanogaster* (Fisher *et al.*, 1982; Lin and Fisher, 1990; Riemer and Weber, 1994) and *Caenorhabditis elegans* (Riemer *et al.*, 1993). However, lamin gene orthologues do not appear to be present in budding or fission yeast genomes. Lamins have also been extensively characterized in *Xenopus laevis* (Krohne *et al.*, 1984, 1987; Stick, 1988, 1992, 1994; Doring and Stick, 1990). In humans, three genes encode nuclear lamins (Biamonti *et al.*, 1992; Lin and Worman, 1993, 1995) (Figure 2). *LMNA* is localized on chromosome 1q21.2 (Wynder *et al.*, 1996), *LMNB1* is on chromosome 5q23.3–q31.1 (Wydner *et al.*, 1996) and *LMNB2* on chromosome 19p13.3 (Biamonti *et al.*, 1992). Orthologous genes at syntenic chromosomal locations are present in mice. *LMNA* encodes the A-type lamins. Lamins A and C arise by alternative splicing of RNA encoded by *LMNA* (Fisher *et al.*, 1986; McKeon *et al.*, 1986; Lin and Worman, 1993) (Figure 2). These proteins are identical for their first 566 amino acids and vary in their carboxyl terminal tails. Lamin A Δ 10, an isoform lacking the amino acids encoded by exon 10, is also generated by alternative RNA splicing (Machiels *et al.*, 1996). Lamins A and C and possibly lamin A Δ 10 are expressed in most somatic cells but are absent from or expressed in diminished quantities in early embryos, some hematopoietic cells, some types of neuron, most undifferentiated epithelial and mesenchymal cells, and several types of cancer (Guilly *et al.*, 1987, 1990; Lebel *et al.*, 1987; Stewart and Burke, 1987; Worman *et al.*, 1988; Rober *et al.*, 1989, 1990; Cance *et al.*, 1992). Lamin C2, a germ cell-specific, arises from alternative splicing of RNA encoded by an alternative first exon of *LMNA* (Furukawa *et al.*, 1994; Alsheimer and Benavente, 1996). Two genes encode B-type lamins. *LMNB1* encodes lamin B1, which seems to be expressed in all somatic cells (Lin and Worman, 1995). *LMNB2* encodes lamin B2, which is expressed in all or most somatic cells (Höger *et al.*, 1990), and lamin B3, a germ cell-specific (Furukawa and Hotta, 1993).

Since its discovery, the nuclear lamina has been thought to play primarily a structural role, supporting the nuclear membranes and the nuclear pore complexes. This putative role was suggested by the filamentous structure of the lamina and the fact that its protein building blocks are intermediate filament proteins. Mouse cells lacking lamin B1 have severely abnormal nuclear morphology (Vergnes *et al.*, 2004). Although some vertebrate somatic cells do not express A-type lamins, cells that normally contain them have abnormalities in nuclear architecture and the mislocalization of integral proteins of the inner nuclear membrane when they are absent (Sullivan *et al.*, 1999; Harborth *et al.*, 2001; Muchir *et al.*, 2003; Nikolova *et al.*, 2004). Such cells also have increased nuclear deformability, decreased mechanical stiffness and decreased viability when subjected to mechanical strain (Broers *et al.*, 2004; Lammerding *et al.*, 2004). Numerous fairly recent studies have also shown that cells expressing mutant A-type lamins have abnormalities in nuclear morphology (Östlund *et al.*, 2001; Raharjo *et al.*, 2001; Vigouroux *et al.*, 2001; Novelli *et al.*, 2002; Bechert *et al.*, 2003; Capanni *et al.*,

2003; Chen *et al.*, 2003; De Sandre-Giovannoli *et al.*, 2003; Eriksson *et al.*, 2003; Favreau *et al.*, 2003; Holt *et al.*, 2003; Mounkes *et al.*, 2003; Csoka *et al.*, 2004a; Goldman *et al.*, 2004; Muchir *et al.*, 2004; Navarro *et al.*, 2004; Reichart *et al.*, 2004, Scaffidi and Misteli, 2005). In addition, cells with certain lamin A/C mutants have increased susceptibility to damage from heat shock (Vigouroux *et al.*, 2001). The lamina also plays a role in anchoring or positioning the nuclear pore complexes, based on their co-purification in a “pore complex-lamina fraction” (Dwyer and Blobel, 1974; Aaronson and Blobel, 1975) and its interaction with Nup153 (Smythe *et al.*, 2000; Hawryluk-Gara *et al.*, 2005). Nuclear lamins may also be involved in the biogenesis or maintenance of the nuclear envelope membranes, as over-expression of prenylated lamins in cells induces excessive nuclear membrane formation and growth (Ralle *et al.*, 2004; Prufert *et al.*, 2004).

Based on its location at the inner nuclear membrane, the lamina has long been thought to anchor chromatin to the nuclear envelope (Figure 1). The binding of lamins to whole chromatin, DNA and histones supports such a function (Luderus *et al.*, 1992, 1994; Glass *et al.*, 1993; Taniura *et al.*, 1995; Goldberg *et al.*, 1999; Stierlé *et al.*, 2003). Lamins have also been implicated in RNA polymerase II-dependent transcription (Kumaran *et al.*, 2002; Spann *et al.*, 2002) and control of DNA replication (Meier *et al.*, 1991; Spann *et al.*, 1997; Moir *et al.*, 2000a). However, the precise spatial coincidence between the intranuclear pool of A-type lamins and DNA replication sites is a matter of debate (Kennedy *et al.*, 2000; Dimitrova and Berezney, 2002; Barbie *et al.*, 2004). Some studies have also implicated lamins in RNA splicing (Jagatheesan *et al.*, 1999; Kumaran *et al.*, 2002) but recent evidence indicates that formation of nuclear splicing compartments is independent of lamins A and C (Vecerova *et al.*, 2004). Since lamins or domains of lamins have not been directly studied in *in vitro* assays of DNA replication, transcription and RNA splicing, their roles in these processes may be indirect, resulting from secondary effects of the pleiotropic functions of lamins. The discoveries described below that mutations lamins A and C cause several different tissue-specific diseases have revealed that the lamina likely plays an important role in the regulation of gene expression, development of certain cell lineages and possibly other critical cellular processes.

C. Inner Nuclear Membrane

The lamina interacts with integral proteins of the inner nuclear membrane. A proteomics analysis has suggested that as many as 80 transmembrane proteins are localized to the inner nuclear membrane in mammalian interphase cells (Schirmer *et al.*, 2003). To date, only approximately a dozen of these proteins have been characterized in detail. Most integral proteins of the inner nuclear membrane have amino-terminal domains that face the nucleoplasm and either single or multiple transmembrane segments. These proteins are synthesized on the rough endoplasmic reticulum membrane and diffuse laterally to reach the inner nuclear membrane, where interactions with the lamina, the chromatin or both retain them (Soullam and Worman, 1993, 1995; Ellenberg *et al.*, 1997; Östlund *et al.*, 1999; Wu *et al.*, 2002). Size constraints imposed by the lateral channels of the nuclear pore complex appear to restrict proteins with

nucleocytoplasmic domains of larger than approximately 60 kDa from reaching the inner nuclear membrane (Soullam and Worman, 1995; Wu *et al.*, 2002). In addition, energy-dependent remodeling of pore complexes may be necessary to allow integral proteins to diffuse through the pore membranes (Ohba *et al.*, 2004).

During mitosis, integral inner nuclear membrane proteins dissociate from the lamina and chromatin and are dispersed into a residual endoplasmic reticulum; they subsequently diffuse in this membrane structure back to decondensing chromatin to reform nuclear envelopes in the daughter cells (Ellenberg *et al.*, 1997; Yang *et al.*, 1997). Like lamins, inner nuclear membrane proteins are phosphorylated on specific sites concurrent with mitotic nuclear envelope disassembly (Courvalin *et al.*, 1992; Foisner and Gerace, 1993; Ellis *et al.*, 1998). Several integral inner nuclear membrane proteins are targeted to decondensing chromatin early in nuclear reassembly, prior to the assembly of the lamina, likely via their interactions with chromatin components (Chaudhary and Courvalin, 1993; Buendia and Courvalin, 1997; Haraguchi *et al.*, 2000). Specific integral proteins of the inner nuclear that have been shown to cause human diseases when mutated are discussed in detail below.

III. Inherited Diseases Caused by Mutations in Nuclear Envelope Proteins

Research on the nuclear envelope took a turn in a new direction in 1994 when the gene mutated in X-linked Emery-Dreifuss muscular dystrophy was identified (Bione *et al.*, 1994). Soon after this discovery, the encoded protein, called emerin, was shown to be an integral inner nuclear membrane protein (Manilal *et al.*, 1996; Nagano *et al.*, 1996). Then, in 1999, mutations in lamins A and C were reported to cause the autosomal dominantly inherited form of Emery-Dreifuss muscular dystrophy (Bonne *et al.*, 1999). Between 1999 and 2004, mutations in A-type lamins were surprisingly shown to cause several other inherited disorders, some affecting striated muscles but others with dramatically different phenotypes. In the past few years, disease-causing mutations have additionally been identified in the protease responsible for prelamin A processing, two other integral proteins of the inner nuclear membrane and an endoplasmic reticulum protein that abnormally concentrates in the perinuclear space when mutated. Despite our gaps in understanding many of their fundamental functions, much of the current research on the nuclear envelope is focused on how mutations in its protein components cause inherited diseases.

A. Perinuclear Space: TorsinA

Dystonia refers to a condition characterized by involuntary, sustained muscle contractions affecting one or more sites of the body. The term torsion describes the twisting nature of body movements observed in subjects with dystonia. Several types of primary inherited torsion dystonias can be distinguished based on their clinical features and genetics (Fahn, 1991). In 1997, Ozelius *et al.* (1997a, 1997b) mapped the locus for an early-onset autosomal dominant dystonia to chromosome 9q34 and demonstrated mutation in the *DYT1* gene encoding an ATPase they called torsinA. Most cases had a

three base pair deletion in the gene that resulted in loss of one of a pair of glutamate residues.

TorsinA is normally localized to the lumen of the endoplasmic reticulum. In 2004, Goodchild and Dauer (2004) and subsequently other groups (Gonzalez-Alegre and Paulson, 2004; Naismith *et al.*, 2004) reported that the disease-causing torsinA mutant is concentrated in the perinuclear space as opposed to the bulk endoplasmic reticulum. Goodchild and Dauer (2005) have recently shown that the disease-causing mutant binds preferentially to the luminal domain of lamina-associated polypeptide 1, an integral protein of the inner nuclear membrane (Senior and Gerace, 1988), while wild type torsinA preferentially binds to a related integral protein of the bulk endoplasmic reticulum membrane.

It is not known how mislocalization of torsinA to the perinuclear spaces leads to damage or death of particular types of neurons. One hypothesis is that it interferes with connections between integral proteins of the inner and outer nuclear membranes that occur within the perinuclear space (Gerace, 2004). Mislocalized torsinA may interfere with these protein-protein interactions (see above), altering proper anchoring of the nucleus to the cytoskeleton. This intriguing hypothesis remains to be tested as a pathogenic mechanism in DYT1 dystonia.

Mutant torsinA has been studied in vertebrate and invertebrate animal models. Transgenic mice overexpressing human mutant torsinA in neurons develop abnormal involuntary dystonic-appearing movements as early as three weeks after birth (Shashidharan *et al.*, 2005). The animals also have hyperkinesias and rapid bi-directional circling. Transgenic mutant torsinA is localized to the nuclear envelope, sometimes in perinuclear inclusions and aggregates (Goodchild and Dauer, 2004; Shashidharan *et al.*, 2005). In *Drosophila*, expression of mutant human torsinA elicits locomotor defects and induces morphological defects at the neuromuscular junctions, some of which resemble those reported in mutants with defects in transforming growth factor-beta signaling (Koh *et al.*, 2004). Null mutations in the *Caenorhabditis elegans* torsinA homologue ooc-5 result in defects in spindle orientation, nuclear rotation and polarity in early embryos (Basham and Rose, 1999, 2001). These animal models suggest possible connections between torsinA, nuclear positioning and possibly transforming growth factor-beta signaling.

B. Integral Inner Nuclear Membrane Proteins

1. LBR

LBR was first identified as a relatively abundant protein in avian erythrocyte nuclear envelopes that bound to B-type lamins, hence its being named lamin B receptor (Worman *et al.*, 1998). Complementary DNA cloning and sequencing has shown that LBR has a basic, amino-terminal domain of approximately 200 amino acids that faces the nucleoplasm followed by a mostly hydrophobic domain with eight putative transmembrane segments (Worman *et al.*, 1990; Ye and Worman, 1994). The human *LBR* gene contains 13 protein-coding exons and is located on chromosome 1q42.1 (Schuler *et al.*, 1994; Wydner *et al.*, 1996).

The nucleoplasmic domain of LBR interacts with B-type lamins (Worman *et al.*, 1988; Ye and Worman, 1994), orthologues of *Drosophila heterochromatin* protein 1 (Ye and Worman, 1996; Ye *et al.*, 1997) and DNA (Ye and Worman, 1994; Duband-Goulet and Courvalin, 2000). Its hydrophobic domain has a high degree of sequence similarity to sterol reductases of the endoplasmic reticulum that are conserved in plants, yeast and animals (Schuler *et al.*, 1994; Holmer *et al.*, 1998). Human LBR has C14-sterol reductase activity when expressed in yeast (Silve *et al.*, 1998). These findings have led to the hypothesis that LBR is a “bi-functional” protein involved in nuclear organization and sterol metabolism. This indeed appears to be the case based on more recent findings in human disorders.

Pelger-Huët anomaly is an autosomal dominantly inherited condition in which the normally hyperlobulated nuclei of peripheral blood granulocytes have two as opposed to the usual five or more lobes that contain coarser and denser heterochromatin (Pelger, 1928; Huët, 1932; Klein *et al.*, 1955). Hoffmann *et al.* (2002) used positional cloning to show that mutations in the *LBR* gene cause this disorder. This has been confirmed in additional subjects (Best *et al.*, 2003). Homozygosity for Pelger-Huët anomaly has been associated with skeletal abnormalities and early lethality (Aznar and Vaya, 1981). Waterham *et al.* (2003) identified a homozygous *LBR* mutation in a human fetus that died *in utero* with Greenberg/HEM skeletal dysplasia. This is a rare, lethal disorder characterized by skeletal dysplasia, severe hydrops, short-limbed dwarfism and marked disorganization of cartilage and bone calcification with a moth-eaten aspect (Greenberg *et al.*, 1988). Waterham *et al.* (2003) also found elevated levels of cholesta-8,14-dien-3-beta-ol in cultured skin fibroblasts of their subject, compatible with a deficiency of the cholesterol biosynthetic enzyme 3-beta-hydroxysterol delta(14)-reductase. Hence, the human clinical syndromes associated with heterozygous and homozygous mutations in *LBR* are consistent with its known associations with chromatin and the lamina and its sequence similarity to other sterol reductases. It appears that having only one copy of wild type *LBR* is compatible with life but leads to a morphological nuclear abnormality only in a particular type of cell with nuclei of a highly specialized shape. On the other hand, loss or mutation of both copies of *LBR* appears to be incompatible with long-term human life but it is not clear if lethality is due to deficiency in a critical sterol reductase activity during fetal development or abnormalities in gene expression that occur as a result of more profound alterations in chromatin organization.

In mice, ichthyosis mutants have mutations in *Lbr* (Shultz *et al.*, 2003). These mice have a blood granulocyte phenotype similar to human Pelger-Huët anomaly but homozygous mutants survive and develop other phenotypic abnormalities, including alopecia, variable expression of syndactyly and hydrocephalus. Inherited Pelger-Huët anomaly has also been reported to occur in rabbits, cats and several breeds of dogs but mutations genetic mutations have not yet been described in these species. Depletion of the *Drosophila* orthologue of LBR by RNA interference in embryos and cultured cells induces no obvious effect on viability or nuclear architecture (Wagner *et al.*, 2004).

2. *MAN1*

The “MAN antigens” were originally identified as three nuclear envelope proteins

recognized by autoantibodies from a human subject with a collagen vascular disease (Paulin-Levasseur *et al.*, 1996). One of the “MAN antigens” was identified as lamina associated polypeptide 2-beta (Lang *et al.*, 1999). This is an integral protein of the inner nuclear membrane with a single transmembrane segment and nucleoplasmic amino-terminal domain that associates with the lamina and chromatin (Foisner and Gerace, 1993). Lin *et al.* (2000) used expression cloning to show that the largest of the “MAN antigens,” MAN1, is a protein of approximately 97 kDa, with a nucleoplasmic amino-terminal domain, two transmembrane segments and a nucleoplasmic carboxyl-terminal domain encoded by a human gene on chromosome 12q14. Sequence analysis showed that MAN1 shares a conserved globular motif of approximately 40 to 50 amino acids near its amino-terminus, termed the LEM domain, with lamina-associated polypeptide 2 and emerin (Lin *et al.*, 2000). It is composed mostly of two large alpha helices and binds to the nucleoplasmic protein barrier-to-autointegration factor (Cai *et al.*, 2001; Laguri *et al.*, 2001; Wolff *et al.*, 2001). The LEM domain has since been found in several other mammalian integral proteins of the inner nuclear membranes and some other nuclear proteins (Schirmer *et al.*, 2003).

Recent work from several laboratories has shown that the carboxyl-terminal domain of mammalian MAN1 and its *Xenopus* orthologues binds to Smad1, Smad2 and Smad3 and antagonize signaling by bone morphogenic protein and transforming growth factor-beta (Osada *et al.*, 2003; Raju *et al.*, 2003; Hellemans *et al.*, 2004; Lin *et al.*, 2005; Pan *et al.*, 2005). Using positional cloning, Hellemans *et al.* (2004) showed that osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis are allelic variants caused by loss-of-function mutations in MAN1. Fibroblasts from subjects with these disorders also showed enhanced expression of transforming growth factor-beta responsive genes (Hellemans *et al.*, 2004). Osteopoikilosis is an autosomal dominant skeletal dysplasia characterized by multiple areas of hyperostotic bone and can occur either as an isolated anomaly or in association with other bone and skin abnormalities (Berlin *et al.*, 1967; Chigira *et al.*, 1991). Buschke-Ollendorff syndrome is the association of osteopoikilosis with disseminated connective-tissue nevi (Buschke and Ollendorff, 1928; Giro *et al.*, 1992). Melorheostosis is characterized by hyperostosis of tubular bone cortex and frequently accompanied by abnormalities of adjacent soft tissues, such as joint contractures, sclerodermatous skin lesions, muscle atrophy and hemangiomas (Campbell *et al.*, 1969; Rozencwaig *et al.*, 1997). Enhanced bone morphogenic protein and transforming growth factor-beta signaling can explain most or all of the phenotypes in these allelic disorders caused by MAN1 mutations.

The phenotype of *Man1* null mice has not yet been reported. Interference with endogenous MAN1 function in *Xenopus laevis* using antisense morpholino oligonucleotides leads to the reduction of anterior neuroectoderm, consistent with enhanced bone morphogenic protein signaling (Osada *et al.*, 2003). In *Caenorhabditis elegans*, RNA interference-mediated removal of approximately 90% of the MAN1 orthologue is lethal in approximately 15% of embryos but those surviving develop into normal fertile adults (Liu *et al.*, 2003). In the absence of the emerin orthologue, approximately 90% reduction of MAN1 in *Caenorhabditis elegans* is lethal to all embryos by the 100-cell stage, with a phenotype involving repeated cycles of anaphase

chromosome bridging and cytokinesis (Liu *et al.*, 2003).

3. *Emerin*

Emery and Dreifuss (1966) described a X-linked form of muscular dystrophy with early contractures of the elbows, Achilles tendons and postcervical muscles, slowly progressive muscle wasting and weakness with a humeroperoneal distribution and cardiomyopathy usually presenting as heart block. Rowland *et al.* (1979) subsequently proposed the term Emery-Dreifuss muscular dystrophy for this condition. In 1994, using positional cloning, Toniolo and associates (Bione *et al.*, 1994) identified a gene on the X chromosome encoding a 254 amino acid protein they named emerin, in honor of Professor Emery, that is mutated in X-linked Emery-Dreifuss muscular dystrophy. Arahata and colleagues (Nagano *et al.*, 1996) and Morris and colleagues (Manilal *et al.*, 1996) subsequently showed that emerin was a nuclear envelope protein lacking from most subjects with X-linked Emery-Dreifuss muscular dystrophy. Sequences in the nucleoplasmic domain of wild type emerin mediate its inner nuclear membrane retention (Östlund *et al.*, 1999; Tsuchiya *et al.*, 1999).

Emerin has a nucleoplasmic amino-terminal domain of 220 amino acids, a single transmembrane segment and a short luminal tail in the perinuclear space. It contains a LEM domain near its amino-terminus (Lin *et al.*, 2000; Wolff *et al.*, 2001). The nucleoplasmic domain of emerin binds to lamins A and C (Fairley *et al.*, 1999; Sullivan *et al.*, 1999; Clements *et al.*, 2000; Sakaki *et al.*, 2001). It also binds to chromatin-associated proteins such as barrier-to-autointegration factor, via its LEM domain, the transcription factor germ cell-less (Lee *et al.*, 2001; Holaska *et al.*, 2003) and Btf, a death promoting transcriptional repressor (Haraguchi *et al.*, 2004). Emerin has also been implicated in capping the pointed ends of actin filaments in the nucleus (Holaska *et al.*, 2004). Despite receiving considerable attention, the physiological significance of these protein-protein interactions and their consequences for disease pathogenesis in cells lacking emerin remain unclear.

In most cases, skeletal and cardiac muscle from patients with X-linked Emery-Dreifuss muscular dystrophy shows a deficiency or a complete lack of emerin (Manilal *et al.*, 1996; Nagano *et al.*, 1996; Ellis *et al.*, 2000; Sewry, 2000; Niebroj-Dobosz *et al.*, 2003). Analysis of cultured fibroblasts from affected subjects or ectopic expression of mutant emerin have emphasized the weakening of the interactions between emerin and A-type lamins (Clements *et al.*, 2000; Ellis *et al.*, 1999; Fairley *et al.*, 1999) that can provoke an increase in the solubility of all lamin types (Markiewicz *et al.*, 2002). However, the spatial chromosome organization studied in the cells of an individual with the X-linked Emery-Dreifuss muscular dystrophy using chromosome painting was not altered (Boyle *et al.*, 2001). Thus, there has been no emergence of a clear model that would explain the pathophysiology of X-linked Emery-Dreifuss muscular dystrophy. Owing to the specific interactions of emerin with A-type lamins, a similar mechanism may be operating for X-linked and autosomal forms of the disease (see below).

The phenotype of emerin-deficient mice has not yet been reported. In *Caenorhabditis elegans*, depletion of the emerin orthologue using RNA interference leads to no detectable phenotype throughout development (Gruenbaum *et al.*, 2002).

Depletion of both the emerin and MAN1 orthologues in *Caenorhabditis elegans* is lethal (Liu *et al.*, 2003).

C. A-type Lamins

1. *Striated Muscle Diseases*

Emery-Dreifuss muscular dystrophy is also inherited as an autosomal dominant disorder, which is clinically identical to the X-linked form (Fenichel *et al.*, 1982; Miller *et al.*, 1985; Emery, 1989). Bonne *et al.* (1999) mapped the locus for autosomal dominant Emery-Dreifuss muscular dystrophy to chromosome 1q11-q23 and showed that mutations in *LMNA* co-segregated with the disease phenotype. These results were the first identification of mutations in A-type nuclear lamins as a cause of an inherited disorder. Subsequently, Fatkin *et al.* (1999) showed that lamin A/C mutations cause a dilated cardiomyopathy with conduction defect, a condition in which the affected subjects have heart abnormalities identical to those in subjects with Emery-Dreifuss muscular dystrophy but minimal or no skeletal muscle involvement. The following year, Muchir *et al.* (2000) reported A-type lamin mutations cause autosomal dominant limb girdle muscular dystrophy type 1B, which also has the same cardiac abnormalities but a different distribution of skeletal muscle involvement. Analyses of additional families showed that these allelic variants could occur in different subjects with the same mutation even within the same family (Bonne *et al.*, 2000; Brodsky *et al.*, 2000). Other atypical patterns of muscle involvement have also been described, as well as significant atypical variability in different subjects with the same mutation (Forissier *et al.*, 2003; Sebillon *et al.*, 2003; Mecuri *et al.*, 2004). Rare *LMNA* compound heterozygotes have also been identified in which Emery-Dreifuss muscular dystrophy is inherited in an autosomal recessive manner (Raffaele Di Barletta *et al.*, 2000). The emerging picture is that certain mutations in A-type lamins cause striated muscle disease characterized by a predominant cardiomyopathy with skeletal muscle either affected in an Emery-Dreifuss pattern, a limb girdle distribution, an atypical pattern or not at all. From a clinical perspective, the cardiomyopathy is the life-threatening component of these disorders caused by *LMNA* mutations (Sanna *et al.*, 2003; Taylor *et al.*, 2003; van Berlo *et al.*, 2005).

Mutations in *LMNA* that cause striated muscle disease are found throughout most of the coding region for lamins A and C (Figure 3). Most are either amino acid substitutions or single amino acid deletions. Some splicing mutations have been identified, as have nonsense mutations early in the coding sequence that result in essential haploinsufficient for lamins A and C. Based on one report of neonatal lethality (van Engelen *et al.*, 2005) and the lack of reports of surviving adults, homozygosity for a single *LMNA* mutation that causes striated muscle disease appears to be incompatible with postnatal human life.

The generation of *Lmna* null mice by Sullivan *et al.* (1999) has provided an informative animal model of Emery-Dreifuss muscular dystrophy. Soon after birth, homozygous *Lmna* null mice show a reduction in their growth rate and develop a cardiac and skeletal myopathy bearing a striking resemblance to the human disease. The cardiac condition is a rapidly progressing dilated cardiomyopathy without

compensatory hypertrophy (Nikolova *et al.*, 2004). More recently, Arimura *et al.* (2005) have generated “knockin” mice carrying a *Lmna* H222P mutation. At adulthood, homozygous mice display reduced locomotion activity with a stiff walking posture, cardiac chamber dilation and hypokinesia with conduction defects. In contrast to affected humans, however, mice with one normal copy of *Lmna* are apparently normal.

2. Partial Lipodystrophy

Lipodystrophies are a heterogeneous group of syndromes characterized by a paucity of adipose tissue often associated with insulin-resistant diabetes mellitus (Reitman *et al.*, 2000). Dunnigan-type familial partial lipodystrophy, also known as lipoatrophic diabetes mellitus and Dunnigan-Köbberling syndrome, is an autosomal dominant disorder characterized by peripheral fat loss, excess central adiposity, insulin resistance and usually type II diabetes mellitus (Dunnigan *et al.*, 1974; Köbberling *et al.*, 1975; Jackson *et al.*, 1997). Some affected subjects have generalized hypertrophy of skeletal muscles (Wildermuth *et al.* 1996; Vantyghem *et al.*, 2004). In 1998, the gene for Dunnigan-type partial lipodystrophy was mapped to chromosome 1q21-22 (Jackson *et al.*, 1998; Peters *et al.*, 1998). This chromosome region contains *LMNA* and subsequently mutations in lamins A and C were identified in affected subjects (Cao and Hegele, 2000; Shackleton *et al.*, 2000; Speckman *et al.*, 2000).

Approximately 90% of the mutations that cause Dunnigan-type partial lipodystrophy are localized in exon 8 of *LMNA*, in particular at codons 482 and 486 (Cao and Hegele, 2000; Shackleton *et al.*, 2000; Speckman *et al.*, 2000; Vigouroux *et al.*, 2000; Garg *et al.*, 2001) (Figure 3). Mutations in exon 11 of *LMNA* at codons 582 and 584 occur in some atypical cases of Dunnigan-type partial lipodystrophy (Speckman *et al.*, 2000; Vigouroux *et al.*, 2000; Garg *et al.*, 2001). A heterozygous amino acid substitution at residue 133 of the lamin A/C rod domain has also been described in a subject with generalized lipoatrophy with insulin-resistant diabetes, hypertriglyceridemia, hepatic steatosis, hypertrophic cardiomyopathy with valvular involvement and disseminated whitish papules (Caux *et al.*, 2003). Two families with Dunnigan-type partial lipodystrophy with mutations in the lamin A/C head domain have also been described that have cardiac conduction system defects and cardiomyopathy (Garg *et al.*, 2002).

Mandibuloacral dysplasia is a rare autosomal recessive disorder, characterized by postnatal growth retardation, craniofacial anomalies, skeletal malformations, mottled cutaneous pigmentation and progeroid features (Young *et al.*, 1971; Zina *et al.*, 1981; Pallotta and Morgese, 1984). In addition, affected individuals have prominent partial lipodystrophy, insulin resistance and diabetes mellitus (Cutler *et al.*, 1991; Freidenberg *et al.*, 1992). Fat loss patterns in mandibuloacral dysplasia has been classified as type A, with loss of subcutaneous fat from the extremities but normal or excess fat in the neck and truncal regions, and type B, with generalized loss of subcutaneous fat involving the face, trunk and extremities (Simha and Garg, 2002). Since individuals with mandibuloacral dysplasia have partial lipodystrophy, Novelli *et al.*, (2002) hypothesized that the disease may be caused by mutations in the *LMNA* gene. They analyzed five consanguineous families and demonstrated linkage to chromosome 1q21 and identified a homozygous missense mutation at amino acid residue 527 of lamin A/C in all of their

affected subjects (Figure 3). The same mutation was subsequently identified in other affected subjects with the type A distribution of fat loss (Shen *et al.*, 2003; Simha *et al.*, 2003).

Although *Lmna* null mice develop cardiomyopathy and skeletal muscular dystrophy, they do not develop partial lipodystrophy or insulin resistance (Sullivan *et al.*, 1999; Cutler *et al.*, 2002). This strongly suggests that partial lipodystrophy does not result from loss of lamin A or C function. Adipocyte loss in lipodystrophies caused by lamin A/C mutations may therefore result from dominant interference with a specific lamin-mediated activity necessary for survival of differentiated adipocytes.

3. Peripheral Neuropathy

Charcot-Marie-Tooth disorders are a group of clinically and genetically heterogeneous hereditary motor and sensory neuropathies, mainly characterized by muscle weakness and wasting, and foot deformities and characteristic electrophysiological and histological changes (Saifi *et al.*, 2003). Type 2 Charcot-Marie-Tooth disorders are defined by a slight or absent reduction of nerve conduction velocities, loss of large myelinated fibers and axonal degeneration. De Sandre-Giovannoli *et al.* (2002), using homozygosity mapping in inbred Algerian families, provided evidence for linkage of an autosomal recessive Charcot-Marie-Tooth type 2 disorder to chromosome 1q21.2-q21.3. They then showed that all affected subjects in these families as well as additional subjects in an unrelated family shared a common homozygous mutation in *LMNA* that led to an amino acid substitution at residue 298 in the lamin A/C rod domain (Figure 3). Subsequent analysis of 21 subjects from seven unrelated Algerian families with the same lamin A/C mutation showed marked variability of the clinical phenotype (Tazir *et al.*, 2004). There is a wide range of age of onset, from six to 27 years, with a mean of 14.4 years. Some affected individuals with disease duration of ten to 15 years had a severe phenotype with distal wasting and weakness of all four limbs and areflexia associated with involvement of the proximal lower limb muscles. Others had a more classical Charcot-Marie-Tooth phenotype with mild functional disability without proximal lower limb involvement after five to 18 years. Electrophysiological studies showed a median motor nerve conduction velocity in the normal range in almost all the subjects and nerve biopsies in six patients revealed severe rarefaction of myelinated fibers and an increased density of demyelinated fibers.

Individuals with Charcot-Marie-Tooth disorders do not typically develop a primary muscular dystrophy or cardiomyopathy. The specific mutation in the rod domain that causes this disease might therefore lead to loss of only one specific function of lamins A and C, which is necessary for proper nerve cell axonal structure or function. *Lmna* null mice develop scoliosis/kyphosis and become hunched, which is evocative of a severe peripheral neuropathy (De Sandre-Giovannoli *et al.*, 2002). This was confirmed by ultrastructural exploration of sciatic nerves that revealed a reduction of axon density, axonal enlargement and the presence of nonmyelinated axons, findings highly similar to those observed in human Charcot-Marie-Tooth type 2 disorders (De Sandre-Giovannoli *et al.*, 2002). Thus *Lmna* null mice develop both muscular dystrophy and axonal neuropathy. Similarly, Walter *et al.* (2005) recently identified a human

mutation in the 5' region of *LMNA* resulting in the loss of 15 nucleotides including the translation ATG initiator codon that segregates in a previously described family with a clinical phenotype that shared features of both Emery-Dreifuss muscular dystrophy and Charcot-Marie-Tooth type 2.

4. Premature Aging Syndromes

Hutchinson-Gilford progeria syndrome is an extremely rare autosomal dominant disorder characterized by striking features of premature aging. Subjects are usually apparently normal at birth but develop signs and symptoms by about a year of age. Prominent signs include the complete or almost complete lack of hair, a disproportionately large head, “pinched” facial features, generalized fat loss, thin skin, incomplete extension at the knees and elbows indicating stiffness of joints and a generally aged appearance (DeBusk, 1972; Brown, 1979). Death from premature coronary artery disease is frequent and may occur in the first decade of life. Hutchinson (1886) was apparently the first to write on this disorder and Gilford (1904) later gave the term progeria to it. DeBusk (1972) may have been the first to call it Hutchinson-Gilford progeria syndrome.

Eriksson *et al.* (2003) localized the gene causing Hutchinson-Gilford progeria syndrome to chromosome 1q by observing two cases of uniparental isodisomy and a case with a six-megabase paternal interstitial deletion. They identified a *de novo* point mutation in exon 11 of *LMNA* that was identical in 18 of 20 classical cases. The mutation is a cytosine to thymidine transition resulting in a silent glycine to glycine change at codon 608 within exon 11 (Figure 3). They identified one additional case with a guanosine to adenine substitution within the same codon. Simultaneously, De Sandre-Giovannoli *et al.* (2003) reported the same cytosine to thymidine transition at codon 608 in two other subjects with Hutchinson-Gilford progeria syndrome. Cao and Hegele (2003) confirmed that five cell lines from subjects with a diagnosis of Hutchinson-Gilford progeria syndrome carried the cytosine to thymidine mutation and another the guanosine to adenine substitution. D'Apice *et al.* (2004) further identified the cytosine to thymidine mutation in three additional families. These *LMNA* mutations create an abnormal splice donor site that generates a mRNA encoding a protein with 50 amino acids deleted from its carboxyl-terminal domain. The amino acids deleted from the mutant protein are unique to prelamin A and not in lamin C. The mutant truncated protein is predicated to contain the CAAX box (CSIM) at its carboxyl-terminus but lack the endoproteolytic cleavage site for conversion to prelamin A, hence it likely remain farnesylated in cells.

Different *LMNA* mutations have been described in individuals with atypical progeria syndromes (Figure 3). In four patients with a diagnosis of atypical Werner syndrome, Chen *et al.* (2003) noted heterozygosity for missense mutations in *LMNA*, specifically at amino acid residues 57, 133 and 140. Csoka *et al.* (2004a) identified heterozygous mutations in three subjects with diagnoses of “atypical Hutchinson-Gilford progeria syndrome,” “severe Werner syndrome” and “Seip syndrome.” Plasilova *et al.* (2004) reported a homozygous lamin A/C mutation in a family with individuals diagnosed with “autosomal recessive Hutchinson-Gilford progeria syndrome,” however;

these individuals may actually have had mandibuloacral dysplasia. Based on the available data, it appears that classical Hutchinson-Gilford progeria syndrome is caused by a cytosine to thymidine, or rarely a guanine to adenine, mutation at codon 608 of *LMNA*. These mutations lead to expression of a truncated prelamin A. Less common atypical conditions with progeroid features may be caused by other lamin A/C mutations.

A progeroid syndrome has been obtained in “knockin” mice homozygous for a proline to leucine substitution at amino acid 530 of lamin A/C (Mounkes *et al.*, 2003). This mutation causes autosomal dominant Emery-Dreifuss muscular dystrophy in humans (Bonne *et al.*, 1999). Mice are normal at birth but rapidly develop severe growth retardation, dying within four to five weeks. Similarities to human progeria include thinning of the skin, hypoplasia and degeneration of cardiac and skeletal muscle, osteoporosis and abnormal dentition. The mechanism of aging in these mice, which could be either an accelerated cell differentiation with premature death or instability to preserve a state of terminal differentiation, has not been elucidated.

5. Other Disorders Caused by Abnormal Prelamin A Processing

As discussed briefly above, prelamin A is processed to lamin A by a series of proteolytic reactions catalyzed by ZMPSTE24 that depend upon protein farnesylation. The steps in prelamin processing are outlined in Figure 4. The first step in prelamin A processing is the addition of farnesyl to the cysteine of the CAAX box at the carboxyl-terminus, which is catalyzed by farnesyl transferase (Sinensky *et al.*, 1994). The second step is the endoproteolytic removal of the last three amino acids by the ZMPSTE24 metalloproteinase, which recognizes the prenylated prelamin A (Leung *et al.*, 2001). In B-type lamins, this step is catalyzed by RCE1 (Maske *et al.*, 2003). The isoprenylated cysteine is then carboxymethylated, a reaction catalyzed by isoprenylcysteine carboxyl methyltransferase (Sinensky *et al.*, 1994; Bergo *et al.*, 2002). Finally, ZMPSTE24 catalyzes a second proteolytic reaction “upstream” to the prenylated cysteine to yield mature lamin A (Kilic *et al.*, 1997; Corrigan *et al.*, 2005). The *LMNA* mutation in classical Hutchinson-Gilford progeria syndrome in fact leads to abnormal processing of prelamin A because the “upstream” ZMPSTE24 endoprotease site is lacking from the truncated mutant protein.

In a woman with mandibuloacral dysplasia with a type B pattern of fat loss who did not have a detectable *LMNA* mutation, Agarwal *et al.* (2003) identified a compound heterozygous mutation in the gene encoding ZMPSTE24. Navarro *et al.* (2004) examined explored nine fetuses and newborn children with restrictive dermopathy, also known as tight skin contracture syndrome. This is a rare disorder characterized by intrauterine growth retardation, tight and rigid skin with erosions, prominent superficial vasculature, small mouth, small pinched nose, micrognathia, sparse eyelashes and eyebrows, mineralization defects of the skull, thin dysplastic clavicles, pulmonary hypoplasia, multiple joint contractures and an early neonatal lethal course. They found that two had a heterozygous splicing mutation in *LMNA*, resulting in expression of a truncated prelamin A protein lacking amino acids also absent from the truncated protein in Hutchinson-Gilford progeria syndrome. The other seven had a heterozygous

insertion introducing a premature termination codon in *ZMPSTE24*. Therefore, it appears that mutations in both A-type lamins and *ZMPSTE24* protease cause diseases with phenotypic overlap, such as mandibuloacral dysplasia, Hutchinson-Gilford progeria syndrome and restrictive dermopathy. A neonatal “tight skin” phenotype has been recently reported in a subject with classical Hutchinson-Gilford progeria syndrome and the cytosine to thymidine mutation at codon 608 of *LMNA* (Sevenants *et al.*, 2005).

Disruption of *Zmpste24* in mice causes lack of processing or prelamin A to lamin A (Leung *et al.*, 2001; Bergo *et al.*, 2002; Pendás *et al.*, 2002). These mice have been reported to have several abnormalities, including retarded growth, alopecia, micrognathia, dental abnormalities, osteolytic lesions in bones and osteoporosis. Some of these phenotypic features are similar to those in human subjects with Hutchinson-Gilford progeria syndrome and mandibuloacral dysplasia. Heterozygosity for *Lmna*-deficiency ameliorates the abnormal phenotype of these mice (Fong *et al.*, 2004).

IV. Pathogenic Mechanisms of Diseases Caused by Mutations in A-type Lamins

One of the most challenging issues facing investigators who study the nuclear envelope is how mutations in A-type lamins result in such a wide range of clinical conditions. Despite major advances in identifying mutations in these diseases, little has been achieved in understanding pathogenic mechanisms. However, information gained from the sites of these mutations in the lamin A and lamin C molecules and the cellular defects observed in cells expressing mutant A-type lamins have led to the development of several hypothetical models of pathogenesis that are the focus of current experimental testing.

A. Location of Mutations in A-type Lamins and Effects on Protein Function

Examination of the locations of disease-causing mutations in the lamin A and lamin C molecules has provided some clues as to why different mutations result in different disease phenotypes. In contrast to individuals with cardiac and skeletal muscle diseases in whom mutations in *LMNA* are located throughout 11 of the 12 exons that encode lamins A and C, most individuals with Dunnigan-type partial lipodystrophy have mutations in exon 8 of *LMNA*, in particular at amino acids 482 and 486 (Figure 3). These amino acids are part of an immunoglobulin-like fold in the carboxyl-terminal tails of lamins A and C. Immunoglobulin folds frequently function in interactions between proteins and in interactions between proteins and nucleic acids.

Information obtained from solving the three-dimensional structure of the lamin immunoglobulin-like fold provides insights into how different mutations in this domain that cause striated muscle disease and those that cause partial lipodystrophy may produce different alterations in protein function (Dhe-Paganon *et al.*, 2002; Krimm *et al.*, 2002). Most of the mutations in the immunoglobulin-like fold in lamins A and C known to cause striated muscle disease occur in conserved hydrophobic residues or in buried conserved polar residues. Thus, mutations that cause muscle diseases appear to destabilize the overall structure of the immunoglobulin-like fold. Striated muscle

diseases also result from mutations in the rod domain of lamin A or C and from all of the frameshift and translation termination mutations described so far. The common effect of mutations in muscle pathology might therefore be destabilization of the entire lamin A and/or lamin C molecule or lamin dimers. This could lead to a global loss of protein function and possibly a destabilization of lamin filaments, consistent with structural or mechanical abnormalities as the primary cellular defect in disease. On the other hand, mutations in the immunoglobulin-like fold that cause Dunnigan-type partial lipodystrophy occur three positions that are close in space and are solvent accessible. These mutations lead to a reduction in the conserved, positively charged character of a surface site defined by these residues. This change in surface charge would not be expected to disrupt protein structure markedly but might perturb the binding of a specific partner, such as a transcription factor, DNA or other chromatin component necessary for adipocyte-specific gene expression.

The information gained from the elegant structural studies of the lamin immunoglobulin-like fold cannot however explain the differences between all mutations reported to cause striated muscle diseases and lipodystrophy (Figure 3). A few of the mutations causing atypical cases of Dunnigan-type partial lipodystrophy are located in a lamin-A specific region, outside of the immunoglobulin-like fold and near the carboxyl-terminus of the protein at amino acids 582 and 584. In addition, two mutations have been reported to cause both partial lipodystrophy and cardiac abnormalities in the same subjects and are located near the amino-terminus of the rod domain of lamins A and C (Garg *et al.*, 2002). It is possible that these regions of lamins A and C interact in some way with the immunoglobulin-like fold but this has not been demonstrated. The mutation causing mandibuloacral dysplasia is also located within the immunoglobulin-like fold at amino acid 527 and changes an arginine to a histidine. Two copies of this mutant allele must be inherited for the disease to occur. Intriguingly, inheriting one mutant *LMNA* allele in which the same arginine is changed to a proline leads to striated muscle disease.

The heterozygous deletions that occur at the carboxyl-terminal end of prelamin A in subjects with Hutchinson-Gilford progeria and restrictive dermopathy could have a double effect on lamin A function. First could be the loss of an amino acid stretch that may have specific interactions. Second, the deletions include the cleavage site for ZMPSTE24 endoprotease that normally trims the several amino acids from prelamin A to generate mature lamin A (Figure 4). Thus, the truncated prelamin A should retain at its carboxyl-terminus a farnesylated and carboxymethylated cysteine residue. The same carboxymethylated and farnesylated cysteine would be retained in wild type prelamin A in subjects with inactivating mutations in ZMPSTE24 endoprotease and normal *LMNA* alleles (Agarwal *et al.*, 2003; Navarro *et al.*, 2004). Ralle *et al.* (2004) and Prufert *et al.* (2004) have shown that the modified CAAX box in B-type lamins is responsible for nuclear membrane growth. Therefore, one can imagine that the abnormal persistence of a similarly modified cysteine residue in truncated or wild type prelamin A could confer to the unprocessed protein a membrane proliferation function. In support of this hypothesis, the nuclear perimeter in cultured cells from subjects with

Hutchinson-Gilford progeria syndrome has a two-fold increase compared to controls, suggesting that excessive membrane biogenesis occurs (Goldman *et al.*, 2004).

Toxicity of posttranslationally modified but unprocessed prelamin A and truncated prelamin A is strongly suggested by recent studies. Long *et al.* (2004) have shown that the phenotype in *Zmpste24* null mice with a normal content in prelamin A is not observed when these mice are crossed to *Lmna* +/- mice, reducing the prelamin A content by half. The latter mice are apparently normal, suggesting that prelamin A is toxic and that reducing its level provides protection from disease. A similar effect has been observed in cultured HeLa cells (Gruber *et al.*, 2005). Using RNA interference, these investigators showed that dramatic changes in nuclear morphology and premature cell death induced by knocking down ZMPSTE24 expression was prevented by knockdown of prelamin A 24 hours earlier. These data confirm that unprocessed prelamin A is a cellular toxin. Using fibroblasts from subjects with Hutchinson-Gilford progeria syndrome, Scaffidi and Misteli (2005) have recently shown that introduction of wild type lamin A protein does not rescue cellular morphological abnormalities. However, upon correction of the aberrant splicing event using a modified oligonucleotide targeted to the activated cryptic splice site, fibroblasts assumed a normal nuclear morphology and proper expression of several misregulated genes was established. The results of these studies strongly suggest that unprocessed prelamin A and the truncated prelamin A in classical Hutchinson-Gilford progeria syndrome are cellular poisons and identify a possible target for therapeutic intervention.

B. Cellular Defects Resulting from A-type Lamin Mutations

Although various abnormalities in nuclear structure in tissues of individuals with mutations in A-type lamins have been reported, their relationship to pathophysiology is unclear. Skeletal muscle from individuals with Emery-Dreifuss muscular dystrophy shows an increase in internal nuclei, with fewer nuclei at the normal location near the periphery of the fibers (Brown *et al.*, 2001; Sewry *et al.*, 2001). However, this is a pathological feature that is common to most muscular dystrophies. There can be an abnormal distribution of heterochromatin in cells from individuals with Emery–Dreifuss muscular dystrophy and lamin A and C mutations but it is not clear whether it is a primary or secondary effect (Sabatelli *et al.*, 2001; Sewry *et al.*, 2001; Fidzianska and Hausmanowa-Petrusewicz, 2003). Nerve biopsies from individuals with Charcot–Marie–Tooth disorder type 2 caused by *LMNA* mutation show a substantial loss of large myelinated fibers and abnormally myelinated axons but their nuclei appear normal (De Sandre-Giovannoli *et al.*, 2002). Studies of affected adipocytes from individuals with Dunnigan-type partial lipodystrophy or mandibuloacral dysplasia have not been published.

Cultured fibroblasts from subjects with mutations in A-type lamins have proven to be useful tools for analyzing morphological disorders induced by the mutations (Novelli *et al.*, 2002; Bechert *et al.*, 2003; Capanni *et al.*, 2003; Chen *et al.*, 2003; De Sandre-Giovannoli *et al.*, 2003; Eriksson *et al.*, 2003; Favreau *et al.*, 2003; Holt *et al.*, 2003; Mounkes *et al.*, 2003; Csoka *et al.*, 2004a; Goldman *et al.*, 2004; Muchir *et al.*, 2004; Navarro *et al.*, 2004; Reichart *et al.*, 2004; Scaffidi and Misteli, 2005). Nuclear defects

in patients affected with diseases other than the progeroid syndromes mainly consist of nuclear herniations that contain A-type lamins and emerin but have a diminished content in nuclear pore complexes and other inner nuclear membrane proteins. Another abnormality that occurs in nuclei of overall normal shape is a polar defect in B-type lamins and other proteins in an area where the lamina network is irregular, sometimes with a honeycomb aspect. Intranuclear aggregates of lamin A have also been observed, most commonly when mutations are in the lamin A/C rod domain. Nuclear abnormalities are generally observed in only a minority of fibroblasts from subjects with *LMNA* mutations and the percentage of affected cells depends upon culture conditions and passage number (Vigouroux *et al.*, 2001; Muchir *et al.*, 2004). Importantly, there is no clear association of a specific cellular phenotype with a particular mutation or with a particular disease (Muchir *et al.*, 2004). Nonetheless, these morphological alterations suggest that the mechanical properties of the nuclear lamina are altered. This has been confirmed by the extensive deformations observed in nuclei when these cells were submitted to heat shock and by the easier chemical extraction of some of their protein components (Vigouroux *et al.*, 2001).

Nuclear abnormalities observed in cultured fibroblasts from subjects with Hutchinson-Gilford progeria syndrome or restrictive dermopathy are sometimes similar to those in cells from subjects with other diseases caused by different lamin A/C mutations (Eriksson *et al.*, 2003; De Sandre-Giovannoli *et al.*, 2003; Goldman *et al.*, 2004; Navarro *et al.*, 2004; Scaffidi and Misteli, 2005). However, some abnormalities appear specific for these diseases, such as a high degree of nuclear lobulation, a large increase in the nuclear perimeter, a thickening of the lamina, a loss of peripheral heterochromatin and clustering of nuclear pore complexes (Goldman *et al.*, 2004). Expression of the truncated prelamin in classical Hutchinson-Gilford progeria in transfected normal cells induces similar changes (Goldman *et al.*, 2004). Mouse embryo fibroblasts from progeroid mice heterozygous for the L530P lamin A/C mutation have morphological abnormalities consistent with the phenotypes observed in fibroblast cell lines from human subjects with autosomal dominantly inherited disorders caused by various *LMNA* mutations (Mounkes *et al.*, 2003). Specific features of cells from these mice are their short lifespan, which is not associated with telomere shortening, and increased apoptosis. Nuclei in cells from *Zmste24* null mice are polylobulated with herniations and similar to nuclei in cells from subjects with progerias (Pendás *et al.*, 2002; Long *et al.*, 2005).

Analysis of cultured fibroblasts from mice and humans that do not express A-type lamins has clearly demonstrated the close association between A-type lamins and emerin and nesprin-alpha2 (Sullivan *et al.*, 1999; Raharjo *et al.*, 2001; Muchir *et al.*, 2004). These two transmembrane proteins of the nuclear envelope are delocalized to the bulk endoplasmic reticulum membrane in cells lacking lamins A and C and relocalized to the inner nuclear membrane after expression of lamin A by transfection. Fibroblasts lacking lamins A and C also have increased nuclear deformability, decreased mechanical stiffness and decreased viability when subjected to mechanical strain (Broers *et al.*, 2004; Lammerding *et al.*, 2004).

Expression of mutant A-type lamins in transfected cultured cells reproduces many of the nuclear envelope abnormalities observed in cells from human subjects and mutant mice (Raharjo *et al.*, 2001; Östlund *et al.*, 2001; Favreau *et al.*, 2003; Holt *et al.*, 2003; Bechert *et al.*, 2003; Goldman *et al.*, 2004). Alterations in transfected cells appear to be caused by a dominant negative effects of the mutant proteins and not to a decrease in the stability of the mutant lamins (Östlund *et al.*, 2001). Delocalization of emerin to the bulk endoplasmic reticulum membrane has also been observed when several lamin A mutants that cause striated muscle diseases are expressed in transfected cells but not when the most common mutant that causes Dunnigan-type partial lipodystrophy is expressed (Östlund *et al.*, 2001; Raharjo *et al.*, 2001; Holt *et al.*, 2003). Cell types that have a lower content of endogenous emerin and A-type lamins appear to be more sensitive to developing nuclear structural alterations when mutated lamins are expressed (Favreau *et al.*, 2003). Studies of the dynamics of mutant A-type lamins using green fluorescent protein fusions and photobleaching methods have shown that the mobility of a lamin A mutant in Dunnigan-type partial lipodystrophy is indistinguishable from wild type lamin A but that three mutants causing striated muscle disease have increased mobility within the nuclear lamina (Gilchrist *et al.*, 2004). Similar studies using fluorescence loss in photobleaching have revealed increased mobility of lamin A and lamin C mutants found in striated muscle diseases as well as in Dunnigan-type partial lipodystrophy (Broers *et al.*, 2005).

C. Hypothetical Models of Pathogenesis

One of the most intriguing issues regarding inherited diseases caused by mutations in nuclear lamins is how mutations in proteins that are expressed in virtually all somatic cells cause different tissue-specific diseases. Although this issue remains to be resolved, as discussed in several previous reviews, investigators in the field appear to have converged on two main hypotheses that will no doubt be the focus of future testing: the “gene expression” hypothesis and the “mechanical stress” hypothesis (Worman and Courvalin, 2000, 2002, 2004; Cohen *et al.*, 2001; Hutchinson *et al.*, 2001; Wilson *et al.*, 2001; Burke and Stewart, 2002; Goldman *et al.*, 2002; Hutchinson and Worman, 2004). Emerging data suggest that aspects of these hypotheses overlap.

The striated muscle phenotype caused by many *LMNA* mutations suggests that defective lamins A and C increase cellular sensitivity to mechanical stress. The nuclear lamina, inner nuclear membrane and nuclear pore complexes are tightly connected in the nuclear envelope. Through filaments attached to the cytoplasmic aspect of the nuclear pore complex, the lamina could be connected indirectly with cytoplasmic intermediate filaments, such as desmin in muscle cells, and thus with the dystrophin-dystroglycan complex of the sarcolemma membrane. Mutations in components of the dystrophin-dystroglycan complex are responsible for several muscular dystrophies (Straub and Campbell, 1997; Cohn and Campell, 2000; Dalkilic and Kunkel, 2003). Electron microscopy of *Lmna* *-/-* mice cardiomyocytes shows a disruption of the cytoskeletal desmin network and its detachment from the surface of the nuclei (Nikolova *et al.*, 2004). We have discussed above the connection of the lamina via integral inner

nuclear membrane proteins of the Sun family to integral proteins of the outer nuclear membrane. Such proteins in the outer nuclear membrane, including nesprins, Zyg12, and Klarsicht, contact actin and microtubule networks. Therefore, the nuclear skeleton and components of the cytoskeleton are connected, determining nuclear position and, when necessary, nuclear migration. Weakness in any component of this integrated cellular skeleton, including the lamina, may make the entire network fragile and the cell more susceptible to damage from recurrent mechanical strain.

Certain genes and signal transduction pathways are activated by mechanical strain. Impaired response to mechanical stimulation can attenuate transcriptional activation of mechanosensitive genes, some of which may be necessary in the heart for the development of compensatory hypertrophy (Nikolova *et al.*, 2004). The role of the lamina in mechano-transduction has been directly investigated by subjecting lamin A and C deficient mouse fibroblasts to mechanical strains (Lammerding *et al.*, 2004). Under strain, these fibroblasts have increased nuclear deformation, defective mechano-transduction, attenuated strain-induced signaling and impaired viability. Thus, the separation between mechanical and gene expression models to explain the cell-specific and tissue-specific alterations in diseases caused by lamin mutations may be artificial and, in fact, abnormalities in response to mechanical stress may lead to aberrant responses in gene activation.

In the “gene expression” hypothesis, lamins A and C are considered essential for the proper tissue-specific expression of certain genes. Dynamic studies have shown that the motion of peripheral chromatin is constrained (Abney *et al.*, 1997; Marshall *et al.*, 1997; Chubb *et al.*, 2002), likely as a result of its association with a stable interphase nuclear lamina-pore complex network (Aaronson and Blobel, 1975; Dwyer and Blobel, 1976; Broers *et al.*, 1999; Moir *et al.*, 2000b; Daigle *et al.*, 2001). Silent genes are located preferentially in this peripheral chromatin whereas expressed genes are usually concentrated in the center of the nucleus (Cremer and Cremer, 2001). Repositioning of a chromatin region from the nuclear periphery to the nuclear core could alter transcriptional activity of genes within the region. Alterations in lamina structure induced by mutations in lamins A and C could therefore perturb normal chromatin compartmentalization and induce tissue-specific changes in gene expression.

The peripheral lamina, particularly A-type lamins, has been shown to play a scaffolding role for several proteins with gene regulatory functions. Lamins form complexes with integral inner nuclear membrane proteins that may immobilize transcription factors and other gene regulatory proteins such as retinoblastoma protein, heterochromatin protein 1, SREBP1, germ cell-less, Oct1, YT521-B and MOK2 (Mancini *et al.*, 1994; Ozaki *et al.*, 1994; Ye and Worman, 1996; Ye *et al.*, 1997; Imai *et al.*, 1997; Nili *et al.*, 2001; Lloyd *et al.*, 2002; Dreuillet *et al.*, 2002; Wilkinson *et al.*, 2003; Holaska *et al.*, 2003; Haraguchi *et al.*, 2004; Johnson *et al.*, 2004). In association with retinoblastoma protein, the A-type lamina network can sequester a large panel of proteins that play a key role in cell cycle progression, such as PCNA, p21, CDK4, and cyclin D3 (Markiewicz *et al.*, 2002, 2005; Favreau *et al.*, 2004). Immobilization of hypophosphorylated retinoblastoma protein on an insoluble nuclear structure is a prerequisite for cell cycle arrest and cell differentiation. Cells lacking lamins A and C

have a dramatic decrease in retinoblastoma protein due to proteosomal degradation, which is restored upon reexpression of lamin A (Johnson *et al.*, 2004). Expression in myoblast cell lines of lamin A with a mutation that causes Emery-Dreifuss muscular dystrophy impairs myotube differentiation in correlation with the persistence of a high level of retinoblastoma protein phosphorylation and a low level of expression of the muscle-specific transcription factor myogenin (Favreau *et al.*, 2004; Markiewicz *et al.*, 2005). This strongly suggests a functional link between the lamina and proteins involved in cell cycle progression and cell differentiation.

V. Concluding Remarks/Future Directions

Our incomplete understanding of the basic functions of lamins and other nuclear envelope proteins makes understanding the pathogenesis of diseases caused by their mutations extremely difficult. Experimental designs have been hampered by the lack of simple “read outs” for the functions of lamins and other proteins. Except for assessing Smad activity in the case of MAN1 mutants and potentially sterol reductase activity in the case of LBR mutants, there are no easily measurable downstream consequences of, for example, abnormal A-type lamin function. Several studies have used nuclear morphology as a marker for A-type lamin function; however, nuclear morphological abnormalities in cells expressing mutant lamins are variable and difficult to quantify.

Future research will be facilitated by the identification of individual genes or functional groups of genes that are dependent on nuclear envelope protein function. Experiments using DNA microarrays have identified genes that are differentially expressed in cells lacking emerin and with mutant A-type lamins; however, the data so far are limited to fairly small studies (Tsukahara *et al.*, 2002; Amati *et al.*, 2004; Csoka *et al.*, 2004b). Nonetheless, gene expression data obtained from DNA microarray studies of fibroblasts from only a small number of subjects with Hutchinson-Gilford progeria syndrome have been useful in examining the “correction” of the abnormal cellular phenotype when reducing the amount of the truncated prelamin A mutant in cells (Scaffidi and Misteli, 2005). Future statistically robust gene expression data obtained using large numbers of human samples and tissues from mouse models should be able to identify important pathways and functional groups of genes that are abnormally activated or repressed when nuclear envelope proteins are mutated or absent. Such results will be tremendously useful for evaluating the effects of mutant nuclear envelope proteins in cellular models of disease.

Animal models deficient in or expressing mutant nuclear envelope proteins have been useful models of human disease. Undoubtedly, additional animal models will be created in the future. Genetically altered mice deficient in nuclear envelope proteins or expressing mutants using either homologous recombination or transgenic approaches will likely be most applicable to understanding human disease physiology. However, as demonstrated by the models already available, all of the features of human disease may not be reproduced in mice. For example, while most of the human diseases caused by A-type lamin mutations are autosomal dominant, heterozygous *Lmna* null mice are apparently normal (Sullivan *et al.*, 1999).

Most importantly, collaborations between a broad range of physicians and scientists with different areas of expertise will be essential for understanding the multiple disorders caused by mutations in lamins and other nuclear envelope. The clinical phenotypes of affected human subjects span the disciplines of neurology, cardiology, endocrinology, metabolism, pediatrics, geriatrics, orthopedics, dermatology, hepatology and hematology. Collection of adequate human cell and tissue samples for experimental studies will require a major coordinated effort between physicians who traditionally have worked in very different areas and basic scientists. The experimental studies themselves will require the efforts of scientists with many different skills, including cell biologists, physiologists, geneticists, biochemists and bioinformaticists. Laudatory efforts to bring together diverse groups of researchers from around the world have been extremely rewarding (Bonne *et al.*, 2002, 2003; Evans *et al.*, 2004; Chadwick and Goode, 2005) and should be encouraged and financially supported in the future.

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Figure Legends

Figure 1. Schematic diagram of the nuclear envelope showing the inner, pore and outer nuclear membranes, the continuous endoplasmic reticulum (ER) membrane, the nuclear lamina and a nuclear pore complex. Integral proteins of the pore membrane include POM121 and gp210, which comprise part of the pore complexes. Representative integral inner nuclear membrane proteins shown are MAN1, LBR, nurim, a SUN protein and another polypeptide with a single transmembrane segment that could represent emerin or one of the lamina-associated polypeptides (LAPs). A nesprin is shown in the outer nuclear membrane with its cytoplasmic calponin homology domain (CH) and its luminal KASH domain, which can interact directly or indirectly with the luminal SUN domain of SUN1 and SUN2. Lamina is represented apposed to the inner nuclear membrane and peripheral heterochromatin, in tight contact with the nuclear pore complex (NPC). The lamina is fenestrated, allowing for the direct contact of the inner nuclear membrane and its integral proteins herein with chromatin. Note that the left side of the nuclear pore complex is not in contact with the pore membrane, representing lateral channels of approximately 10 nm in diameter, which allow for diffusion of integral proteins synthesized on the rough endoplasmic reticulum membrane to the inner nuclear membrane.

Figure 2. Nuclear lamins and their genes. *LMNA* on chromosome 1 encodes lamin A and lamin C (as well as a minor isoform lamin A Δ 10 and a germ cell isoform lamin C2, not shown). Lamins A and C are identical for their first 566 amino acids; lamin C contains 6 unique amino acids (white rectangle) and lamin A 98 unique amino acids. *LMNB1* on chromosome 5 encodes lamin B1. *LMNB2* on chromosome 19 encodes lamin B2 (and a germ cell isoform lamin B3, not shown). The lamin proteins contain head and tail domains (thin lines) and alpha helical central rod domains (gray rectangles). Lamins contain a nuclear localization signal (NLS) in their tail domains. All lamins except lamin C (and C2) contain a CAAX box (CAAM) at their carboxyl-termini, which is a signal for farnesylation (squiggly line). A protease cleaves off the three terminal amino acids (double headed arrow) as part of the prenylation reaction (the cysteine is also carboxymethylated in the process). Prelamin A is also cleaved “upstream” from the prenylated cysteine (double headed arrow to the left) in a second proteolytic reaction to yield mature lamin A.

Figure 3. Schematic diagram of prelamin A showing the nature and locations of disease-causing mutations. Thin gray rectangle at left is the head domain, thicker blue rectangles the rod domain and thin gray rectangle at right the tail domain; these sequences are common to lamins A and C. The nuclear localization signal is represented by light blue. The orange striped area at the far right represents sequence absent from lamin C. Mutations that cause the striated muscle diseases Emery-Dreifuss muscular dystrophy (EDMD, red), limb girdle muscular dystrophy type 1B (LGMD1B, orange) and dilated cardiomyopathy with conduction defect (DCM-CD, pink) are shown above the schematic diagram of the molecule. Mutations causing Charcot-

Marie-Tooth disorder type 2A (CMT2A, dark red), Dunnigan-type familial partial lipodystrophy (FPLD, dark green), lipodystrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy (LILLC, light green), mandibuloacral dysplasia (MAD, purple), Hutchinson-Gilford progeria syndrome (HGPS, dark blue), Seip syndrome (Seip, light blue) and atypical Werner syndrome (AWS, lighter blue) are shown below the schematic diagram of the molecule. The R28W and R62G mutations shown for FPLD are atypical cases with cardiac disease; 90% of cases have mutations at either residue 482 or 486. For HGPS, the classical cases have either the G608G mutation or, more rarely, the G608S mutation; the others have been reported in atypical cases.

Figure 4. Schematic diagram outlining the steps in the processing of prelamin A to lamin A. Amino acids in prelamin A encoded by part of *LMNA* exon 11 and exon 12 are shown. See text for details.

Figure 1

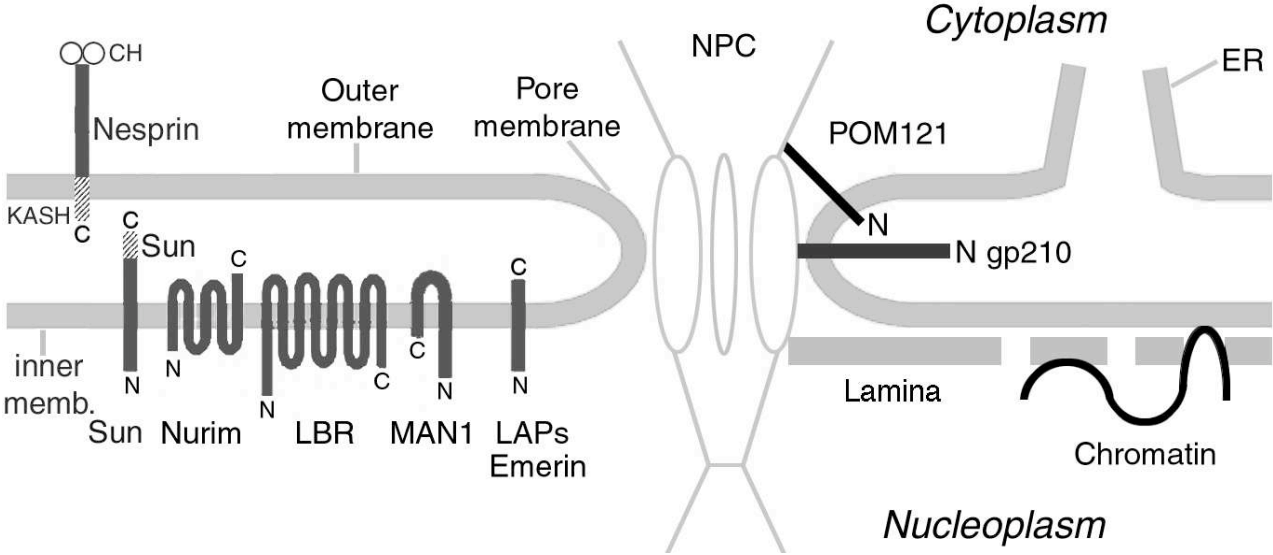


Figure 2

Chr / Genes Lamins

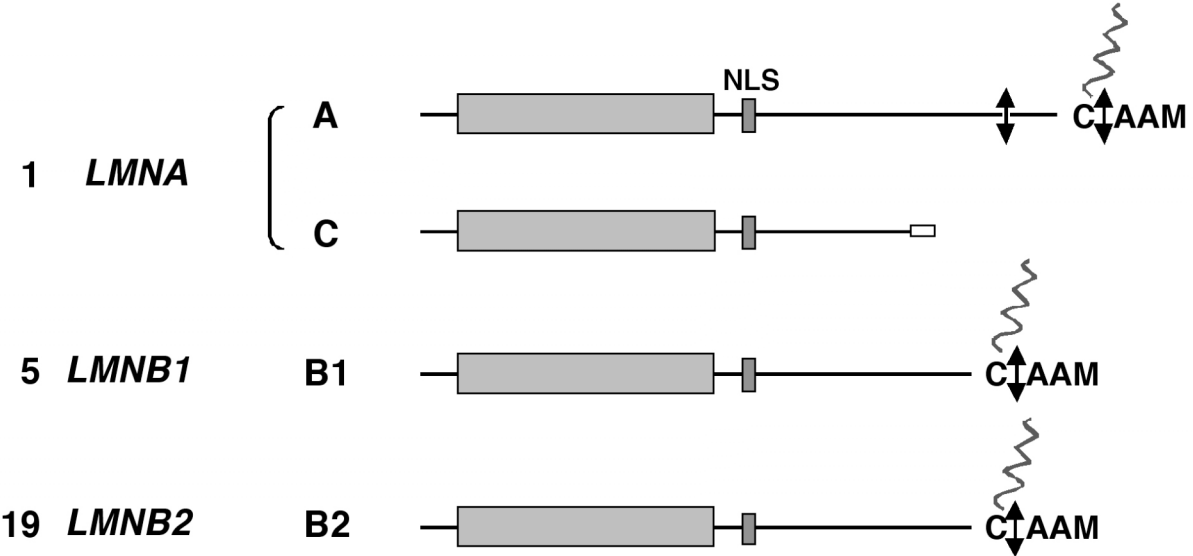


Figure 3

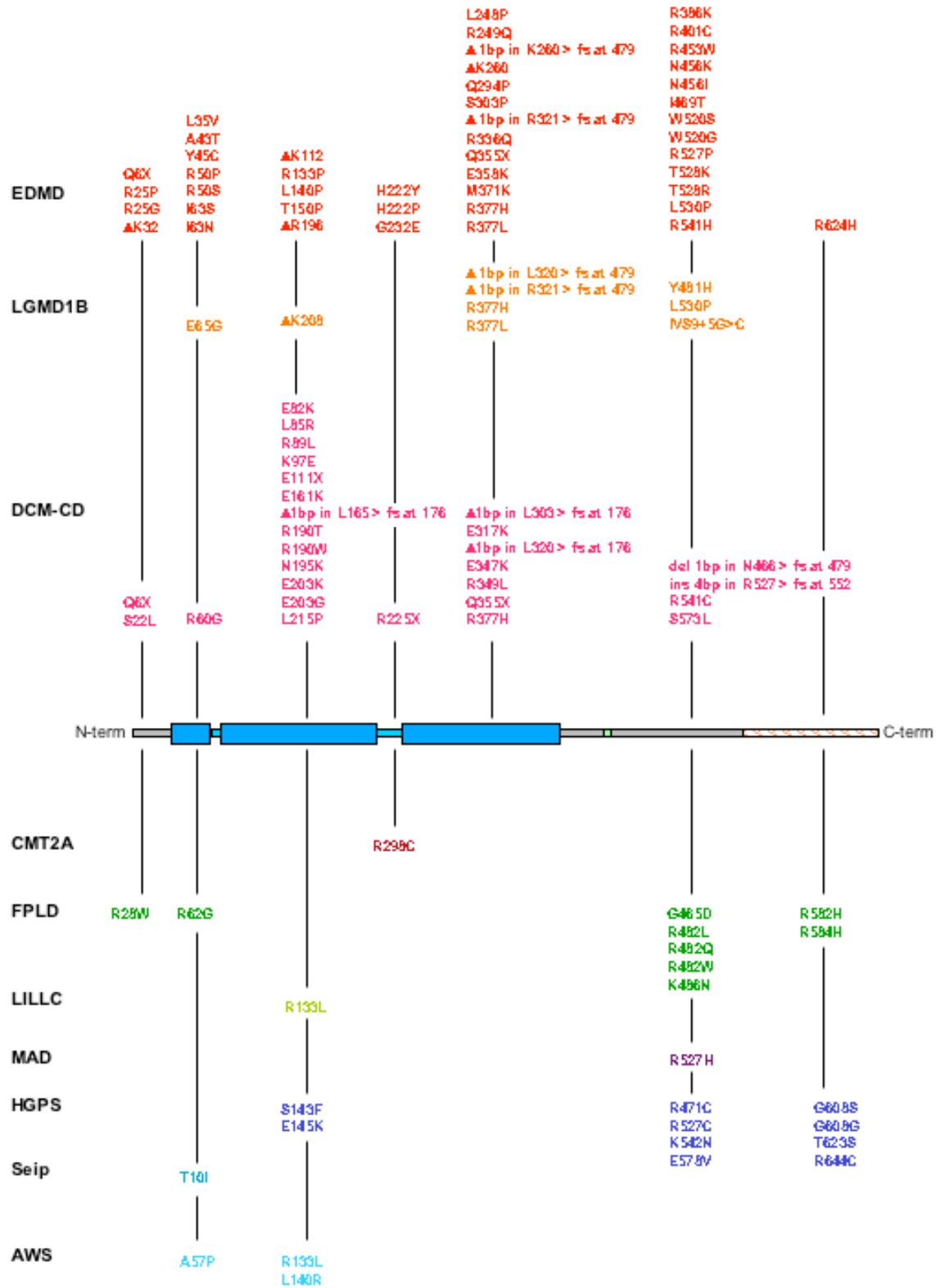


Figure 4

