In the past decade, a wide range of fascinating monogenic diseases have been linked to mutations in the \textit{LMNA} gene, which encodes the A-type nuclear lamins, intermediate filament proteins of the nuclear envelope. These diseases include dilated cardiomyopathy with variable muscular dystrophy, Dunnigan-type familial partial lipodystrophy, a Charcot-Marie-Tooth type 2 disease, mandibuloacral dysplasia, and Hutchinson-Gilford progeria syndrome. Several diseases are also caused by mutations in genes encoding B-type lamins and proteins that associate with the nuclear lamina. Studies of these so-called laminopathies or nuclear envelopathies, some of which phenocopy common human disorders, are providing clues about functions of the nuclear envelope and insights into disease pathogenesis and human aging.

Mutations in \textit{LMNA} encoding the A-type lamins cause a group of human disorders often collectively called laminopathies. The major A-type lamins, lamin A and lamin C, arise by alternative splicing of the \textit{LMNA} pre-mRNA and are expressed in virtually all differentiated somatic cells. Although the A-type lamins are widely expressed, \textit{LMNA} mutations are responsible for at least a dozen different clinically defined disorders with tissue-selective abnormalities. Mutations in genes encoding B-type lamins and lamin-associated proteins, most of which are similarly expressed in almost all somatic cells, also cause tissue-selective diseases.

Research on the laminopathies has provided novel clues about nuclear envelope function. Recent studies have begun to shed light on how alterations in the nuclear envelope could explain disease pathogenesis. Along with basic research on nuclear structure, the nuclear lamins, and lamina-associated proteins, clinical research on the laminopathies will contribute to a complete understanding of the functions of the nuclear envelope in normal physiology and in human pathology.

\textbf{LMNA: ONE GENE, MANY DISEASES}

George Beadle and Edward Tatum (Beadle and Tatum 1941) proposed what became known as the “one gene-one enzyme” hypothesis and was later modified to the “one gene-one polypeptide” hypothesis. The premise underlying this hypothesis was that genes act through the production of polypeptides, with each gene producing a single polypeptide functioning in
a particular step in a metabolic pathway or other cellular process. A corollary of this hypothesis, which formed the foundation of most early studies using positional cloning to identify disease genes, was the “one gene-one disease” principle. We now know that this is not correct and perhaps the best example that disproves this principle is \textit{LMNA}.

\textit{LMNA} encoding the A-type lamins was characterized in 1993 and subsequently mapped to chromosome 1q21.2-q21.3 (Lin and Worman 1993; Wydner et al. 1996). The first human disease identified by positional cloning to be caused by \textit{LMNA} mutations was autosomal dominant Emery-Dreifuss muscular dystrophy (Bonne et al. 1999). Rare compound heterozygous mutations in \textit{LMNA} causing recessively inherited Emery-Dreifuss muscular dystrophy were described shortly thereafter (Raffaele di Barletta et al. 2000). Patients with Emery-Dreifuss muscular dystrophy classically have early contractures of the elbows, Achilles tendons, and posterior neck, rigidity of the spine, slowly progressive muscle weakness in the upper arms and lower legs, and dilated cardiomyopathy with an early onset atrioventricular conduction block (Emery 2000; Muchir and Worman 2007).

Soon after \textit{LMNA} mutations were shown to cause Emery-Dreifuss muscular dystrophy, mutations in this gene were shown to cause other dominantly inherited diseases affecting primarily striated muscle, including dilated cardiomyopathy 1A (Fatkin et al. 1999) and limb-girdle muscular dystrophy type 1B (Muchir et al. 2000). Like Emery-Dreifuss muscular dystrophy, these conditions have a predominant dilated cardiomyopathy with early onset atrioventricular conduction block. In dilated cardiomyopathy 1A, skeletal muscle is minimally affected or unaffected. In limb-girdle muscular dystrophy, the distribution of skeletal muscle involvement is primarily around the shoulders and hips with sparing of the distal extremities. Most subjects with limb-girdle muscular dystrophy do not have joint contractures characteristic of classical Emery-Dreifuss muscular dystrophy. It was originally proposed that Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy 1A, and limb-girdle muscular dystrophy type 1B resulted from different mutations in \textit{LMNA}. However, the phenotypic variability is most likely because of the influence of modifier genes or environmental factors. This is suggested by intrafamilial variability and phenotypic overlap in patients with \textit{LMNA} mutations and muscle disease (Bonne et al. 2000). Within a single family, one affected individual can be diagnosed with isolated cardiomyopathy, another with Emery-Dreifuss muscular dystrophy, and others with limb-girdle muscular dystrophy (Brodky et al. 2000). Based on the combined phenotypic and genetic data, dilated cardiomyopathy with variable skeletal muscle involvement, a phrase used by Brodsky et al. (2000), is a very appropriate descriptor of the striated muscle disease caused by \textit{LMNA} mutations.

Although most \textit{LMNA} mutations causing muscle disorders present during childhood or early adulthood, rare subjects present with congenital muscular dystrophy (Quijano-Roy et al. 2008). Congenital muscular dystrophy has an earlier onset and more severe phenotype than the later-onset muscle disorders caused by \textit{LMNA} mutations. Most cases of \textit{LMNA}-associated congenital muscular dystrophy are caused by de novo mutations but cases of germinal mosaicism have also been identified (Makri et al. 2009). Although some of the \textit{LMNA} mutations causing congenital muscular dystrophy appear to be unique, others have been reported in patients with the later-onset myopathies. A unique \textit{LMNA} splice site mutation has also been associated with a heart-hand syndrome, which is characterized by the association of congenital cardiac disease and limb deformities (Renou et al. 2008).

After \textit{LMNA} mutations were shown to cause striated muscle diseases, a surprising discovery was made regarding another monogenic disease affecting different tissues. In 1998, the genetic locus for Dunnigan-type familial partial lipodystrophy had been mapped using positional cloning to chromosome 1q21-22 (Jackson et al. 1998; Peters et al. 1998). Lipodystrophies are a group of disorders characterized by the absence or reduction of subcutaneous adipose
tissue. Patients with Dunnigan-type familial partial lipodystrophy, a dominantly inherited disorder, are born with normal fat distribution but after the onset of puberty there is regional loss of fat from the extremities associated with insulin resistance and frequently diabetes mellitus (Dunnigan et al. 1974). Knowing that the genetic locus for this disease was at chromosome 1q21-22, Cao and Hegele (2000) hypothesized that the analogy between the regional muscle wasting in autosomal dominant Emery-Dreifuss muscular dystrophy and the regional adipocyte degeneration in this disease made LMNA a candidate gene. They identified a novel missense mutation in exon 8 leading to a R482Q amino-acid substitution, which cosegregated with the lipodystrophy phenotype in five Canadian families. At around the same time, the two groups that had mapped the disease to chromosome 1q21-22 performed finer mapping and identified the LMNA R482Q and other mutations in exon 8 leading to amino-acid substitutions (Shackleton et al. 2000; Speckman et al. 2000). Missense mutations in exon 11 of LMNA leading to R582H and R584H amino-acid substitutions in lamin A, but not lamin C, were further identified in some atypical cases (Speckman et al. 2000; Vigouroux et al. 2000).

Subsequently, there have been a few reports of patients with other LMNA mutations with atypical lipodystrophy syndromes, sometimes in combination with muscle abnormalities (Vigouroux and Capeau 2005). By 2000, the positional cloners had clearly shown that mutations in LMNA cause two quite different diseases: dilated cardiomyopathy with variable muscular dystrophy and partial lipodystrophy. However, the situation soon became more complicated when just a couple of years later De Sandre-Giovannoli et al. (2002) performed homozygosity mapping in inbred Algerian families with an autosomal recessive form of Charcot-Marie-Tooth disease type 2, linked it to chromosome 1q21.2-q21.3, and identified a LMNA mutation leading to the R298C amino-acid substitution. Subjects with Charcot-Marie-Tooth disease type 2 diseases, including the subtype caused by LMNA mutation, have slight or absent reduction of nerve conduction velocities, loss of large myelinated fibers, and axonal degeneration (Chaouch et al. 2003). Affected individuals with the R298C mutation have variable severity and progression of disease, suggesting that modifier genes influence the phenotype of peripheral neuropathy caused by LMNA mutation (Tazir et al. 2004). Later in 2002, Novelli et al. (2002) hypothesized that LMNA mutations might cause mandibuloacral dysplasia, a rare autosomal recessive disorder in which subjects have an undersized jaw, underdeveloped clavicles, other congenital bone abnormalities, and partial lipodystrophy. They studied five consanguineous Italian families and identified a homozygous LMNA missense mutation causing a R527H amino-acid substitution that was shared by all affected patients. Subsequent subjects have been described with homozygous LMNA mutations causing R527C or A529V amino-acid substitutions (Agarwal et al. 2008; Garg et al. 2005). A compound heterozygous subject for the LMNA R527H and a V440M mutation with some features of mandibuloacral dysplasia, lack of muscle strength, and decreased muscle tone has also been reported (Lombardi et al. 2007).

Hutchinson-Gilford progeria syndrome, first described over a century ago, is a rare disease with features of accelerated or premature aging (Hutchinson 1886; Gilford 1904; McKusick 1952; DeBusk 1972). Individuals with this autosomal dominant sporadic syndrome generally die in the second decade of life from myocardial infarction or stroke (DeBusk 1972; Merideth et al. 2008). Other prominent phenotypic features are sclerotic skin, joint contractures, prominent eyes, an undersized jaw, decreased subcutaneous fat, alopecia, skin dimpling and mottling, prominent vasculature in the skin, fingertip tufting, and growth impairment (Merideth et al. 2008). In 2003, Francis Collins and colleagues localized the responsible gene to chromosome 1q by observing two cases in which this chromosomal region was from the same parent and one case with a six-megabase paternal interstitial deletion (Eriksson et al. 2003). They then showed that 18 out of 20 classical cases of Hutchinson-Gilford progeria...
had a de novo G608G (nucleotide 1824 C>T) mutation within exon 11 of LMNA and another case with a G608S (nucleotide 1822 G>A) mutation (Eriksson et al. 2003), a finding that was simultaneously reported by De Sandre-Giovannoli et al. (2003) and then confirmed by Cao and Hegele (2003). These mutations activate a cryptic splice donor site resulting in the synthesis of a protein with 50 amino acids deleted near the carboxy terminus of prelamin A. This truncated prelamin A variant is not appropriately processed to lamin A. Other LMNA missense mutations not generating abnormal RNA splicing within exon 11 have also been reported in variant progeroid syndromes (Chen et al. 2003; Csoka et al. 2004; Verstraeten et al. 2006). Mandibuloacral dysplasia caused by LMNA mutations, as discussed previously, also has progeroid features.

In summary, genetic studies since the late 1990s have shown that mutations in LMNA cause about a dozen clinical disorders with different names (Table 1). These can more broadly be classified into diseases affecting predominantly (1) striated muscle, (2) adipose tissue, (3) peripheral nerve, or (4) multiple tissues resulting in progeroid phenotypes. These mostly tissue-selective disorders occur even though A-type lamins are intermediate filament protein components of the nuclear lamina in virtually all differentiated somatic cells.

**Table 1. Mutations in LMNA cause several distinct clinical diseases predominantly affecting striated muscle, adipose, and peripheral nerve, or give a progeria phenotype**

<table>
<thead>
<tr>
<th>Striated Muscle</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant (and rarely recessive)</td>
<td>Emery-Dreifuss muscular dystrophy</td>
</tr>
<tr>
<td>Cardiomyopathy dilated 1A</td>
<td>Limb-girdle muscular dystrophy type 1B</td>
</tr>
<tr>
<td>Congenital muscular dystrophy</td>
<td>“Heart-hand” syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td></td>
</tr>
<tr>
<td>Dunnigan-type familial partial lipodystrophy</td>
<td>Lipodystrophy with diabetes and other features of insulin resistance</td>
</tr>
<tr>
<td>Atypical lipodystrophy syndromes</td>
<td>Mandibuloacral dysplasia*</td>
</tr>
<tr>
<td>Peripheral Nerve</td>
<td></td>
</tr>
<tr>
<td>Charcot-Marie-Tooth disease type 2B1</td>
<td></td>
</tr>
<tr>
<td>Progeria Phenotype</td>
<td></td>
</tr>
<tr>
<td>Hutchinson-Gilford progeria syndrome</td>
<td>Atypical Werner Syndrome</td>
</tr>
<tr>
<td>Variant progeroid disorders</td>
<td>Mandibuloacral Dysplasia*</td>
</tr>
</tbody>
</table>

*Mandibuloacral dysplasia has features of lipodystrophy and progeria

**OTHER LAMINOPATHIES/NUCLEAR ENVELOPATHIES**

Monogenic diseases resulting from mutations in genes encoding B-type lamins and proteins that are directly or indirectly associated with the nuclear lamina are also sometimes referred to as laminopathies or nuclear envelopathies (Table 2). Emery-Dreifuss muscular dystrophy was shown to be inherited in an X-linked manner years before autosomal inheritance was described (Emery and Dreifuss 1966). In its classical presentation, the X-linked inherited disease phenocopies the autosomal form. In 1994, Daniella Toniole and colleagues reported that the gene responsible for X-linked Emery-Dreifuss muscular dystrophy encoded a monomeric transmembrane protein expressed in virtually all cells that the authors named emerin (Bione et al. 1994). They extended their initial findings to more patients (Bione et al. 1995). Soon after, emerin was shown to be a protein of the inner nuclear membrane (Manilal et al. 1996; Nagano et al. 1996). Emerin was further shown to depend on A-type lamins for its localization to the nuclear envelope and to directly interact with lamins (Clements et al. 2000; Fairley et al. 1999; Sullivan et al. 1999). The clinical spectrum of disease resulting from mutations in EMD encoding emerin is actually wider than the classical Emery-Dreifuss phenotype and includes a limb-girdle muscular dystrophy, cardiomyopathy with minimal muscle or joint involvement, and various intermittent forms (Astejada et al. 2007).

Lamin B receptor is an integral protein of the inner nuclear membrane that binds to B-type lamins (Worman et al. 1988). It has a basically charged, nucleoplasmic, amino-terminal domain that binds to lamins, DNA, and...
chromatin proteins followed by a stretch of eight putative transmembrane segments that has high sequence similarity to sterol reductases (Worman et al. 1990; Ye and Worman 1994, 1996; Holmer et al. 1998). Heterozygous mutations in

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMD</td>
<td>emerin</td>
<td>cardiomyopathy with muscular dystrophy</td>
</tr>
<tr>
<td>LBR</td>
<td>lamin B receptor</td>
<td>Pelger-Huët anomaly (heterozygous)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Greenberg skeletal dysplasia (homozygous)</td>
</tr>
<tr>
<td>LEMD3</td>
<td>MAN1</td>
<td>Sclerosing bone dysplasias</td>
</tr>
<tr>
<td>SYNE1</td>
<td>nesprin-1</td>
<td>cerebellar ataxia</td>
</tr>
<tr>
<td>TMPO</td>
<td>lamina-associated</td>
<td>cardiomyopathy*</td>
</tr>
<tr>
<td></td>
<td>polypeptide 2</td>
<td></td>
</tr>
<tr>
<td>TOR1A</td>
<td>torsinA</td>
<td>DYT1 dystonia</td>
</tr>
<tr>
<td>LMNB1</td>
<td>lamin B1</td>
<td>adult-onset autosomal dominant leukodystrophy</td>
</tr>
<tr>
<td>LMNB2</td>
<td>lamin B2</td>
<td>acquired partial lipodystrophy</td>
</tr>
<tr>
<td>ZMPSTE24</td>
<td>prelamin A endoprotease</td>
<td>restrictive dermopathy and progeroid disorders</td>
</tr>
</tbody>
</table>

*Reported in two affected individuals in a single family without gene sequencing from unaffected individuals in the same family.

Table 2. Diseases caused by mutations in genes encoding B-type lamins or proteins associated with the nuclear lamina

In one case, a homozygous mutation leading to production of a truncated protein lacking the carboxyl-terminal 82 amino acids was reported to cause hydrops-ectopic calcification—“moth-eaten” or Greenberg skeletal dysplasia, a lethal disorder, which was associated with loss of detectable sterol Δ14-reductase activity (Waterham et al. 2003). It appears that depending on the amount of expression and the affected functional domains of the protein, the phenotypes resulting from mutations in LBR can range from a benign alteration in neurophil nuclear morphology to death in utero.

MAN1 is an integral inner nuclear membrane protein with two transmembrane segments and two nucleoplasmic domains (Lin et al. 2000). The nucleoplasmic domain preceding the first transmembrane segment has been reported to bind to A-type lamins, B-type lamins, and emerin (Mansharamani and Wilson, 2005). The nucleoplasmic domain following the second transmembrane segment binds to regulatory-Smads and DNA (Hellemans et al. 2004; Lin et al. 2005; Pan et al. 2005; Caputo et al. 2006). Heterozygous loss-of-function mutations in LEMD3 encoding MAN1 cause osteopoikilosis, Buschke-Ollendorff syndrome, and nonsporadic melorheostosis, sclerosing bone dysplasias that sometimes have hyperproliferative skin abnormalities. These phenotypes are likely associated with enhanced transforming growth factor-β and bone morphogenic protein signaling, the effects of which are mediated by regulatory-Smads.

SYNE1 encodes nesprin-1, a protein with several isoforms that arise by alternative RNA splicing. Depending on their size, nesprin-1 isoforms may localize to the inner or outer nuclear membrane. Larger nesprin-1 isoforms localize to the outer nuclear membrane and interact in the perinuclear space with Sun proteins, integral proteins of the inner nuclear membrane that bind to lamins, forming a complex connecting the nucleus to the cytoskeleton (Crisp et al. 2006). Homozygous mutations in SYNE1 have been shown to cause an autosomal recessive cerebellar ataxia specifically affecting a part of the brain (Gros-Louis et al. 2007). In one large family, however, a SYNE1 mutation was shown to cosegregate with autosomal...
recessive arthrogryposis, a disease characterized by bilateral clubfoot, decreased fetal movements, and delayed motor milestones with progressive motor decline after the first decade (Attali et al. 2009).

Mutations in genes encoding other proteins that interact directly or indirectly with lamins also cause tissue-selective human diseases. Polymorphisms in the gene encoding lamina-associated polypeptide 2 have been identified in two individuals with cardiomyopathy in a single family; however, sequencing of the gene in unaffected family members was not reported (Taylor et al. 2005). DYT1 dystonia is a central nervous system movement disorder in which sustained muscle contractions lead to twisting and repetitive movements or abnormal postures; it is caused by an in-frame deletion in TOR1A encoding torsinA that leads to loss of a glutamic acid residue (ΔE302/3) from the protein (Ozelius et al. 1997). TorsinA is an AAA+ ATPase of the endoplasmic reticulum that interacts with the luminal domain of lamina-associated polypeptide 1, an integral inner nuclear membrane protein that interacts with lamins (Goodchild and Dauer 2005). The torsinA ΔE302/3 variant concentrates in the perinuclear space relative to the bulk endoplasmic reticulum (Gonzalez-Alegre and Paulson 2004; Goodchild and Dauer 2004; Naismith et al. 2004), where it appears to selectively disrupt the structure of the nuclear envelopes of neurons (Goodchild et al. 2005).

Mutations in genes other than LMNA but directly affecting lamins also cause diseases. ZMPSTE24 is an endoprotease responsible for the processing of prelamin A to lamin A (see later). Loss-of-function mutations in ZMPSTE24 cause autosomal recessive restrictive dermopathy, a neonatal lethal progeroid disorder (Navarro et al. 2005). Compound heterozygous mutations in ZMPSTE24 also cause progeroid disorders with some cases being diagnosed as mandibuloacral dysplasia (Agarwal et al. 2003; Shackleton et al. 2005). Duplication of LMNB1 encoding lamin B1 leading to increased expression of the protein causes adult onset autosomal dominant leukodystrophy, a slowly progressive neurological disorder characterized by symmetrical widespread myelin loss in the central nervous system (Padiath et al. 2006). Heterozygous mutations or polymorphisms in LMNB2 encoding lamin B2 have been also reported in patients with acquired partial lipo- dystrophy (Hegele et al. 2006).

Overall, a number of human disorders have been described that are caused by mutations in genes encoding lamins and associated nuclear envelope proteins. This number is likely to continue to grow over time. Achalsia-Addisonianism-alacrima syndrome, familial atrial fibrillation, infantile bilateral striatal necrosis, and infection-triggered acute necrotizing encephalopathy have also been shown to result from mutations in genes encoding proteins of the nuclear pore complex, a major component of the nuclear envelope that mediates nucleocytoplasmic transport (Tullio-Pelet et al. 2000; Cronshaw and Matunis 2003; Basel-Vanagaite et al. 2006; Zhang et al. 2008; Neilson et al. 2009).

NUCLEAR ENVELOPE FUNCTION AND DISEASE PATHOGENESIS

Studies of laminopathies have provided insights into novel functions of the nuclear envelope. Perhaps most significantly, these studies strongly suggest that the intermediate filament nuclear lamina, although serving as a structural support for the nuclear membranes, must have additional functions. Because very different disease phenotypes can result from alterations in lamins, the nuclear lamina likely has cell-type and tissue-selective properties.

Like all intermediate filament proteins, A-type lamins have a relatively small head domain, a conserved α-helical rod domain, and a tail domain. Lamins A and C are identical for the first 566 amino acids, sharing the head, rod, and first portion of the tail domain, with lamin C having six unique carboxy-terminal amino acids and prelamin A having 98 unique carboxy-terminal residues. Examination of the predominant genotype-phenotype correlations for alterations in lamin A structure strongly suggests that different domains of the proteins have different tissue-selective functions (Fig. 1). Most mutations that cause striated muscle
diseases lead to amino-acid substitutions, small deletions, splice site alterations, or truncations throughout lamins A and C. Approximately 90% of the mutations that cause Dunnigan-type familial partial lipodystrophy generate amino-acid substitutions within an immunoglobulin-type fold in the tails of lamins A and C. Most mutations causing peripheral neuropathy lead to the R298C substitution in the rod domain and most mutations causing mandibuloacral dysplasia generate amino-acid substitutions at or very near amino-acid residue 527 in the immunoglobulin-type fold. Classical Hutchinson-Gilford progeria syndrome is caused by mutations within exon 11 of LMNA, leading to an in frame deletion of 50 amino acids from the tail of prelamin A.

The distribution of LMNA mutations causing striated muscle diseases suggests that these lead to a defect in overall lamina structure in cells. Homozygous Lmna knockout mice develop regional skeletal and cardiac muscle abnormalities within the first 2 months of life and their heterozygous littermates develop...
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cardiomyopathy with conduction block at much older ages (Sullivan et al. 1999; Wolf et al. 2008). Heterozygous mutations leading to significant lamin truncations in humans also cause striated muscle disease (Bonne et al. 1999; Jakobs et al. 2001; MacLeod et al. 2003). Expression of missense lamin A variants that cause muscle disease disrupts the structure of the nuclear lamina and leads to morphological alterations similar to those in cells from which A-type lamins are depleted (Östlund et al. 2001; Raharjo et al. 2001). Transgenic expression of a lamin A variant encoded by a LMNA mutation that causes cardiomyopathy and muscular dystrophy in humans alters lamina structure and induces severe heart disease in mice (Wang et al. 2006). These observations suggest that muscle disease results either from a partial loss of A-type lamins or expression of variants that “dominantly interfere” with the overall structure and function of the nuclear lamina.

It remains generally accepted that one function of the lamina is to provide structural support to the nuclear envelope. One hypothesis for the pathogenesis of striated muscle disease is that a defective lamina fails to properly carry out this support function. Fibroblasts from Lmna knockout mice, transfected cells that express lamin A variants and fibroblasts from human subjects with LMNA mutations and muscle diseases, all have abnormal nuclear morphology at the light microscopy level (Sullivan et al. 1999; Östlund et al. 2001; Raharjo et al. 2001; Muchir et al. 2004). Fibroblasts from Lmna knockout mice also have decreased mechanical stiffness (Broers et al. 2004; Lammerding et al. 2004; Lee et al. 2007). Abnormalities in the nuclear lamina could even potentially affect cytoskeleton functions, as the lamina is connected to cytoplasmic actin via the nesprin isoforms and Sun proteins that span the perinuclear space (Crisp et al. 2006). Depletion of A-type lamins indeed disrupts cytoskeletal processes such as cellular migration and nuclear positioning (Lee et al. 2007; Houben et al. 2009).

In hearts and to a lesser extent in skeletal muscle from Lmna H222P knockin mice, a model of Emery-Dreifuss muscular dystrophy, there is abnormal activation of the MAP kinases ERK1/2 and JNK (Muchir et al. 2007b). These MAP kinases are activated by mechanical stress in cardiomyocytes (Baines and Molkentin 2005). Chronically increased ERK and JNK activation is detrimental to hearts and treatment of Lmna H222P knockin mice with an inhibitor of ERK signaling prevents development of cardiomyopathy (Muchir et al. 2009). Altered nuclear envelope elasticity is also caused by loss of emerin, which binds to A-type lamins, and this could contribute to increased nuclear fragility in humans subjects with mutations in EDM and striated muscle disease (Rowat et al. 2006). ERK is also abnormally activated in hearts of mice lacking emerin (Muchir et al. 2007a). Structural alterations in the nuclear envelope and connected cytoskeleton resulting from LMNA or EDM mutations may therefore make cells such as cardiomyocytes highly susceptible to damage by recurrent mechanical stress, leading to the activation of stress-response pathways that are further detrimental to cells over time.

Data from subjects with Dunnigan-type familial partial lipodystrophy suggest that the immunoglobulin-type fold in the tail of A-type lamins has specific functions in adipose cells. LMNA mutations responsible for approximately 90% of cases lead to amino-acid substitutions that decrease the positive charge of a solvent-exposed surface on the immunoglobulin-type fold but are not predicted to alter the three-dimensional structure of lamins (Dhe-Paganon et al. 2002; Krimm et al. 2002). However, they affect the ability of the immunoglobulin-type fold of A-type lamins to bind to DNA (Stierlé et al. 2003) and could potentially alter binding of a protein important in adipocyte differentiation or survival. These mutations have in fact been shown to decrease an interaction between lamin A and SREBP1 (Lloyd et al. 2002); however, the physiological consequences of this interaction remain to be shown. LMNA mutations that cause Dunnigan-type familial partial lipodystrophy may result in a “gain of function,” as overexpression of either lamin A with a causative amino-acid change or wild-type lamin A both block differentiation of preadipocytes in adipocytes in vitro.
(Boguslavsky et al. 2006) and deficiency of A-type lamins does not cause lipodystrophy in mice (Cutler et al. 2002). The immunoglobulin-type fold of A-type lamins may therefore negatively regulate adipocyte differentiation, or survival "gain of function" may cause partial lipodystrophy. Mandibuloacral dysplasia, which has partial lipodystrophy as a predominant feature, also results from amino-acid substitutions in the immunoglobulin-type fold; however, there are other abnormalities affecting different tissues in this autosomal recessive disease requiring inheritance of two mutant LMNA alleles.

Perhaps the best example of a laminopathy providing insights into nuclear envelope protein function is what progeroid disorders have taught us about the need for proper prelamin A processing. Since the early 1980s, it has been recognized that lamin A is synthesized as a precursor molecule prelamin A (Gerace et al. 1984). Prelamin A contains a CaaX motif at its carboxyl terminus, a sequence known to initiate three sequential chemical reactions (Clarke 1992; Zhang and Casey 1996; Young et al. 2005). In the first reaction, the cysteine of the carboxy-terminal CaaX motif is farnesylated by protein farnesyltransferase. In the second reaction, the –aaX is clipped off. In the third, the farnesylcysteine is methylated by isoprenylcysteine carboxyl methyltransferase. The role of these three reactions in prelamin A processing is shown in Figure 2.

Initially, the groups of Klaus Weber and Michael Sinensky showed that processing of prelamin A resulted from cleavage of an isoprenylated, specifically farnesylated, polypeptide 15 amino acids away from the carboxy-terminal cysteine (Weber et al. 1989; Beck et al. 1990; Sinensky et al. 1994). Sinensky’s group then characterized a farnesylation-dependent prelamin A endoprotease activity in cells (Kilic et al. 1997). In 2002, the groups of Stephen Young and Carlos López-Otín reported that mice deficient in zinc metalloproteinase ZMPSTE24 were defective in the processing of prelamin A to lamin A (Bergo et al. 2002; Pendás et al. 2002). In 2005, Sinensky’s group confirmed in vitro using recombinant ZMPSTE24 that this endoprotease clips the –aaX from prelamin A and catalyzes the second cleavage that removes the remaining 15 carboxy-terminal amino acids (Corrigan et al. 2005). Removal of the –aaX from prelamin A is likely

Figure 2. Processing of prelamin A to mature lamin A in wild-type (WT) cells occurs in several steps, described in the text (middle column). In restrictive dermopathy (RD), the ZMPSTE24 enzyme is nonfunctioning, resulting in accumulation of farnesylated prelamin A (left column). In Hutchinson-Gilford progeria syndrome (HGPS), the second cleavage site for ZMPSTE24 is deleted, resulting in accumulation of a truncated form of farnesylated prelamin A (right column).
redundantly catalyzed by the enzyme RCE1 (Young et al. 2005).

The LMNA mutation causing Hutchinson-Gilford progeria syndrome that activates a cryptic splice site in exon 11 leads to an in frame deletion of 50 amino acids that contains the second ZMPSTE24 endoproteolytic site in prelamin A (De Sandre-Giovannoli et al. 2003; Eriksson et al. 2003). As a result, a farnesylated, truncated prelamin A variant that cannot be properly processed accumulates in cells (Fig. 2). Loss of ZMPSTE24 activity leads to accumulation of unprocessed, farnesylated prelamin A (Fig. 2), which causes restrictive dermopathy and other progeroid disorders that have clinical overlap with Hutchinson-Gilford progeria syndrome. Zmpste24 knockout mice have progeroid features that overlap with mice having a targeted knockin mutation of Lmna that causes Hutchinson-Gilford progeria syndrome (Yang et al. 2006). Blocking farnesylation of the truncated prelamin A or unprocessed prelamin A in these mice with chemical inhibitors improves the mouse phenotypes (Fong et al. 2006; Yang et al. 2006; Varela et al. 2008). Similarly, heterozygosity for Lmna deficiency eliminates the progeria-like phenotypes in Zmpste24 knockout mice (Fong et al. 2004). These results indicate that accumulation of farnesylated prelamin A or the truncated variant plays a key role in the pathogenesis of the progeroid phenotype.

It is less clear how accumulation of farnesylated prelamin A polypeptides lead to progeria phenotypes. Cultured cells expressing these proteins have microscopic abnormalities in nuclear morphology and blocking protein farnesyltransferase activity significantly reverses these abnormalities (Eriksson et al. 2003; De Sandre-Giovannoli et al. 2003; Bridger and Kill 2004; Goldman et al. 2004; Paradisi et al. 2005; Yang et al. 2005; Capell et al. 2005; Glynn and Glover 2005; Mallampalli et al. 2005; Toth et al. 2005; Young et al. 2005; Wang et al. 2008). These nuclear morphological abnormalities are associated with reduced deformability of the lamina and increased stiffness of the nucleus (Dahl et al. 2006; Verstraeten et al. 2008). However, alterations in nuclear morphology and nuclear mechanics are not unique to progeroid syndromes and occur as a result of LMNA mutations that cause other laminopathies. Expression of farnesylated prelamin A or the truncated variant in Hutchinson-Gilford progeria syndrome perturb DNA damage response and repair, leading to genomic instability (Liu et al. 2005), but inhibition of protein farnesylation does not appear to reduce DNA double-strand breaks or damage checkpoint signaling (Liu et al. 2006). Cells accumulating these isoprenylated A-type lamins also have altered signaling pathways involved in regulating stem cell behavior (Espada et al. 2008; Scaffidi and Misteli 2008).

Although accumulation of isoprenylated prelamin A polypeptides is important in progeria pathogenesis, genetic studies show that it is not the entire explanation. Some atypical progeroid disorders resulting from LMNA mutations are not associated with accumulation of prelamin A (Verstraeten et al. 2006). Furthermore, Yang et al. (2008) elegantly showed that expression in mice of a nonfarnesylated variant of the truncated prelamin A in Hutchinson-Gilford progeria syndrome nonetheless causes a progeroid-like phenotype, albeit less severe than that in mice expressing the farnesylated protein. Hence, alterations in A-type lamins other than accumulation of isoprenylated forms can lead to the same cellular defects that give rise to progeroid phenotypes.

CONCLUDING REMARKS

Are studies of the rare monogenic laminopathies relevant to common human diseases and physiological aging? Some data suggest that this might indeed be the case. As patients with familial dilated cardiomyopathies have been screened for genetic causes at some medical centers, LMNA mutations have been shown to be responsible for approximately ten percent of all cases and a third with atrioventricular conduction block (Arbustini et al. 2002; Taylor et al. 2003; van Tintelen et al. 2007; Parks et al. 2008). Compared with other dilated cardiomyopathies, those caused by LMNA mutations are associated with the rapid development of heart failure, early life-threatening arrhythmias, and
sudden death (Bécane et al. 2000; Taylor et al. 2003; van Berlo et al. 2005; Pasotti et al. 2008). Hence, screening for LMNA mutations as part of the clinical routine could provide information that leads to early placement of a pacemaker and an implantable cardioverter defibrillator to prevent sudden death (Meune et al. 2006).

Given that mutations in genes encoding nuclear envelope proteins cause rare monogenic diseases, it is possible that polymorphic variants of the same genes predispose or contribute quantitatively to the development of common diseases. As LMNA mutations cause rare lipodystrophy disorders, several groups have examined if LMNA polymorphisms contribute to the development of common disorders. Although not completely conclusive, some studies suggest that polymorphic variations in LMNA may predispose to insulin resistance, diabetes mellitus, and metabolic syndrome (Duesing et al. 2008; Steinle et al. 2004; Wegner et al. 2007; Owen et al. 2007; Mesa et al. 2007; Murase et al. 2002). Hence, subtle alterations in A-type lamins may contribute to the pathogenesis of diseases that are endemic in the developed world. One could similarly hypothesize that polymorphisms in genes encoding other nuclear envelope proteins could contribute to other common diseases. For example, subtle alterations in MAN1, loss of function of which causes sclerosing bone dysplasias, could hypothetically contribute to the development of osteoporosis.

The involvement of A-type lamins in the pathogenesis of progeroid syndromes has raised interest about their role in physiological aging. The abnormal RNA splicing occurring as a result of the LMNA mutations that cause Hutchinson-Gilford progeria syndrome takes place at very low levels in normal cells (McClintock et al. 2007; Scaffidi and Misteli 2006). One study has shown that the truncated prelamin A that results from this RNA splicing event accumulates in dermal fibroblasts and keratinocytes in older individuals (McClintock et al. 2007). Fibroblasts from older normal subjects have also been reported to show defects similar to those in cells from subjects with Hutchinson-Gilford progeria syndrome, such as abnormal nuclear morphology, increased DNA damage, and changes in histone modifications (Scaffidi and Misteli 2006). These findings support a hypothesis that low-level expression of the truncated prelamin A generated as a result of the LMNA mutation that causes Hutchinson-Gilford progeria syndrome may contribute to aspects of physiological aging.

In closing, a word of caution is warranted about extrapolating data from laminopathies to common diseases. For example, children with Hutchinson-Gilford progeria syndrome have normal cognitive and other brain functions, whereas central nervous system degeneration is a major feature of normal human aging. Elevated blood levels of total cholesterol, C-reactive protein, and low density lipoprotein do not appear to contribute to the accelerated vascular occlusive disease in Hutchinson-Gilford progeria syndrome (Gordon et al. 2005) and affected vessels show pathological features that are unusual for typical atherosclerosis (Stehbens et al. 1999). Hence, Hutchinson-Gilford progeria syndrome may not be a perfectly accurate model to understand some of the major complications of physiological human aging. Similarly, other laminopathies that share phenotypic features with common human disorders may have different underlying pathogenic mechanisms. Nonetheless, research on this fascinating group of rare diseases is clearly providing clues about fundamental functions of the nuclear envelope as well as relevant insights into cellular processes that must be at least partly involved in certain aspects of common diseases and aging.

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REFERENCES

H.J. Worman, C. Östlund, and Y. Wang


Laminopathies and Aging


H.J. Worman, C. O¨ stlund, and Y. Wang


# Diseases of the Nuclear Envelope

Howard J. Worman, Cecilia Östlund and Yuexia Wang

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