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The Nuclear Envelope as a Signaling Node in Development and Disease

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The development of a membrane-bound structure separating DNA from other cellular components was the epochal evolutionary event that gave rise to eukaryotes, possibly occurring up to 2 billion years ago. Yet, this view of the nuclear envelope as a physical barrier greatly underestimates its fundamental impact on cellular organization and complexity, much of which is only beginning to be understood. Indeed, alterations of nuclear envelope structure and protein composition are essential to many aspects of metazoan development and cellular differentiation. Mutations in genes encoding nuclear envelope proteins cause a fascinating array of diseases referred to as "nuclear envelopathies" or "laminopathies" that affect different tissues and organ systems. We review recent work on the nuclear envelope, including insights derived from the study of nuclear envelopathies. These studies are uncovering new functions for nuclear envelope proteins and underlie an emerging view of the nuclear envelope as a critical signaling node in development and disease.

Introduction

Despite the common cartoon image of the nucleus as a symmetrical sphere, a quick glance at a textbook of histology or the results from a Google Image Search makes it obvious that there is great diversity of nuclear shape and that striking differences exist in the nuclear structure of metazoan cells. These differences exist both between cell types and within a single cell type at different stages of differentiation. For example, there are striking differences between the largely spherical neuronal nucleus and the highly lobulated nucleus of the peripheral blood neutrophil (Figure 1). Additionally, both of these cell types have very differently shaped nuclei at earlier stages of differentiation: migrating neurons have highly irregular and distorted-appearing nuclei, whereas the myeloblastoid precursor of the neutrophil is a regular spheroid (Figure 1). While these structural alterations in nuclear shape have been known for decades, little is known about the underlying mechanisms or the biological significance of these events.

Similarly enigmatic are the compositional and consequent functional differences that exist between the nuclear envelopes of different cell types. The fact that tissue-specific disease commonly results from mutations in genes encoding widely expressed nuclear envelope proteins is evidence of cell-type-specific differences in nuclear envelope function. Most notable are the tissue-specific diseases that result from mutations in *LMNA*, the gene encoding the widely expressed A-type lamins. *LMNA* mutations cause a range of clinical disorders that affect different tissues and some (the progerias) that even affect the aging process itself, highlighting the many crucial functions localized to the nuclear envelope. The best-appreciated nuclear-envelope-localized function is that of nucleocytoplasmic transport, mediated by nuclear pore complexes. Yet, new studies have identified novel functions of nuclear pore proteins (nucleoporins), including roles in cell division, transcriptional regulation, and signaling. Indeed, an emerging body of work supports a new view of the nuclear envelope as a node that integrates and transduces a range of signals during development and in terminally differentiated cells. Hence, beyond its classical barrier function, studies of the nuclear envelope are increasingly providing insights into basic aspects of cellular organization and function and providing novel insights into the pathogenesis of human disease.

Nuclear Envelope Alterations in Development and Differentiation

The striking diversity and plasticity of nuclear morphology implies that there are mechanisms that control the shape and protein composition of the nuclear envelope. Dissecting these pathways would likely lead to the discovery of new mechanisms that control development and differentiation and perhaps shed light on the biological reasons for the marked changes in nuclear morphology that are observed between cell types and during cell differentiation. Moreover, given the frequent association of nuclear shape changes with human disease—both with the rare nuclear envelopathies (see below) as well as prevalent diseases such as cancer—knowledge of these pathways should be helpful in unraveling the potential pathogenic significance of these morphological observations. This issue of *Developmental Cell* contains detailed reviews of the nuclear pore complex and the protein complexes that link the nucleoskeleton and cytoskeleton (the LINC complexes). In this Review, we therefore focus our discussion on in vivo studies exploring the dynamic changes known to occur at the nuclear envelope and loss-of-function studies in worm, fly, and mouse that link nuclear

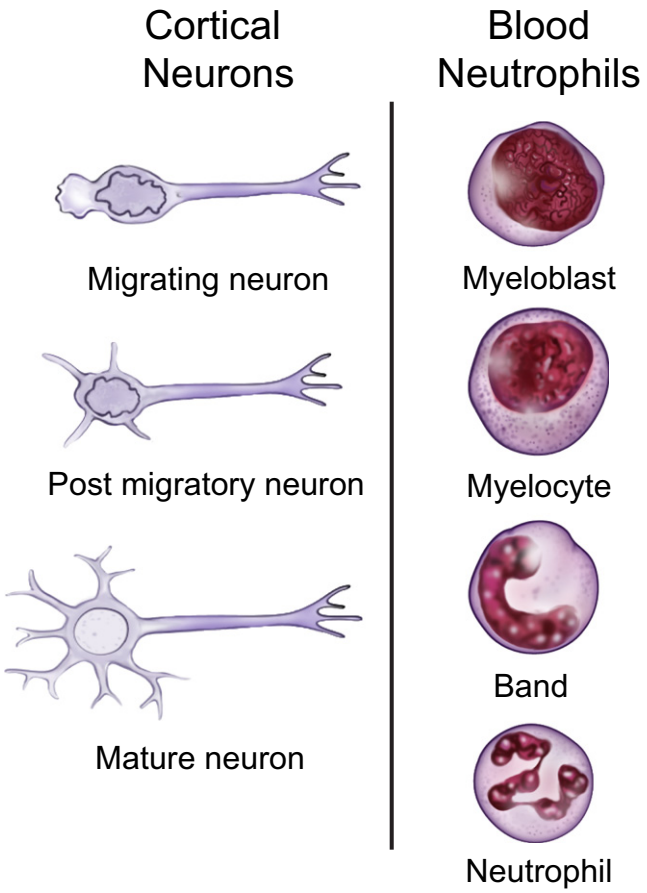

Figure 1. Differences in Nuclear Shape during Cellular Differentiation and in Terminally Differentiated Cells

The developing cortical neuron (left) and the blood neutrophil (right) exhibit differences in nuclear morphology. There are striking differences between the largely spherical adult neuronal nucleus and the highly lobulated mature neutrophil nucleus. Both of these cells also have very differently shaped nuclei at earlier stages of differentiation: migrating neurons having irregular distorted-appearing nuclei, whereas the precursors of the mature neutrophil have more spheroidal nuclei. Diagrams of cortical neurons are based upon micrographs in Goodchild et al. (2005).

envelope proteins to pathways that control development or differentiation.

Nucleoporins

A varying requirement for nucleocytoplasmic transport makes it intuitive that signaling pathways must exist that control the number and composition of nuclear pores between different cell types and at different stages of development. Early observational studies using electron microscopy documented differences in the number and density of nuclear pores between different cell types. For example, there is a 5-fold increase in neuronal nuclear pore number between the 18th prenatal and 15th postnatal days in mice, followed by a gradual decrease to steady-state levels around the 180th postnatal day (Lodin et al., 1978). Later observations in vitro linked the number of nuclear pores to transcriptional or nucleocytoplasmic transport activity (Maul et al., 1980). In cycling cells, the number of nuclear pore complexes also doubles during S phase in preparation for mitosis. Some of the mechanisms underlying the dynamic behavior of pore complexes are beginning to be uncovered in a large body of work performed in yeast and cultured cell lines; this work has identified specific nucleoporins that are critical for nuclear pore assembly and maintenance and has demonstrated the existence of distinct transport pathways (see Hetzer and Wente, 2009).

Although many nucleoporins are nonessential in yeast (Fabre and Hurt, 1997), the genetic deletion of most nucleoporins causes early embryonic lethality in worms, flies, or mice, demonstrating the critical role played by the nuclear pore complex during metazoan development. Despite these early lethal phenotypes, examination of the embryos, or cells derived from them, has yielded interesting insights into the role of the pore complex in basic cell biological processes. For example, RNA interference (RNAi)-mediated knockdown of multiple nucleoporins in the worm *Caenorhabditis elegans* all led to a similar defect in spindle orientation at the two cell stage (Schetter et al., 2006), suggesting that these proteins function in a common process, perhaps related to the connection of the cytoskeleton to the nuclear surface. Deletion of Nup98 in mice led to lethality at embryonic day 6.5 to 7.5, and assessment of these embryos suggested a role for these nucleoporins in gastrulation (Wu et al., 2001). Interestingly, loss of Nup98 specifically impaired cytoplasmically oriented nucleoporins and led to a selective defect in transport of proteins with a nuclear localization signal (Wu et al., 2001). Deletion of Nup96 also leads to early lethality in mice, but characterization of cells from *Nup96*$^{+/-}$ mice demonstrates a role for this protein (and the Nup107-160 complex to which it belongs) in the control of cell-cycle progression (Chakraborty et al., 2008). Interestingly, *Nup96*$^{+/-}$ mice also show a defect in innate and adaptive immunity, in part related to impaired T cell proliferation (Faria et al., 2006), illustrating how a fundamental defect (proliferation) can cause a relatively tissue-specific phenotype, depending upon the tissue's functional characteristics.

Cell-specific or developmental-stage-specific protein expression are additional mechanisms that can lead to tissue-specific phenotypes. A number of studies have documented nuclear pore proteins with such expression differences, most notably in the developing nervous system. Genetic deletion of Nup133 or Nup50 in mice both cause lethality at approximately embryonic day 9.5 and a kinked neural tube that fails to close normally (exencephaly), in addition to other abnormalities (Lupu et al., 2008; Smitherman et al., 2000). Although both of these nucleoporins exhibit widespread expression in the embryo, the expression of both is markedly higher in the neural tube. Lupu et al. (2008) also demonstrated defects in neuronal differentiation in vivo and showed that embryonic stem cells from these mice are selectively inefficient in neuronal differentiation, suggesting a specific role for this nucleoporin in neuronal differentiation. Differentiation-stage-dependent differences in expression of karyopherin/importin-α have also been implicated in the progression of neural differentiation (Yasuhara et al., 2007).

Nuclear Lamina

The nuclear lamina is a meshwork of intermediate filaments that resides on the inner aspect of the inner nuclear membrane and is composed of proteins called lamins (Gerace et al., 1978; Aebi

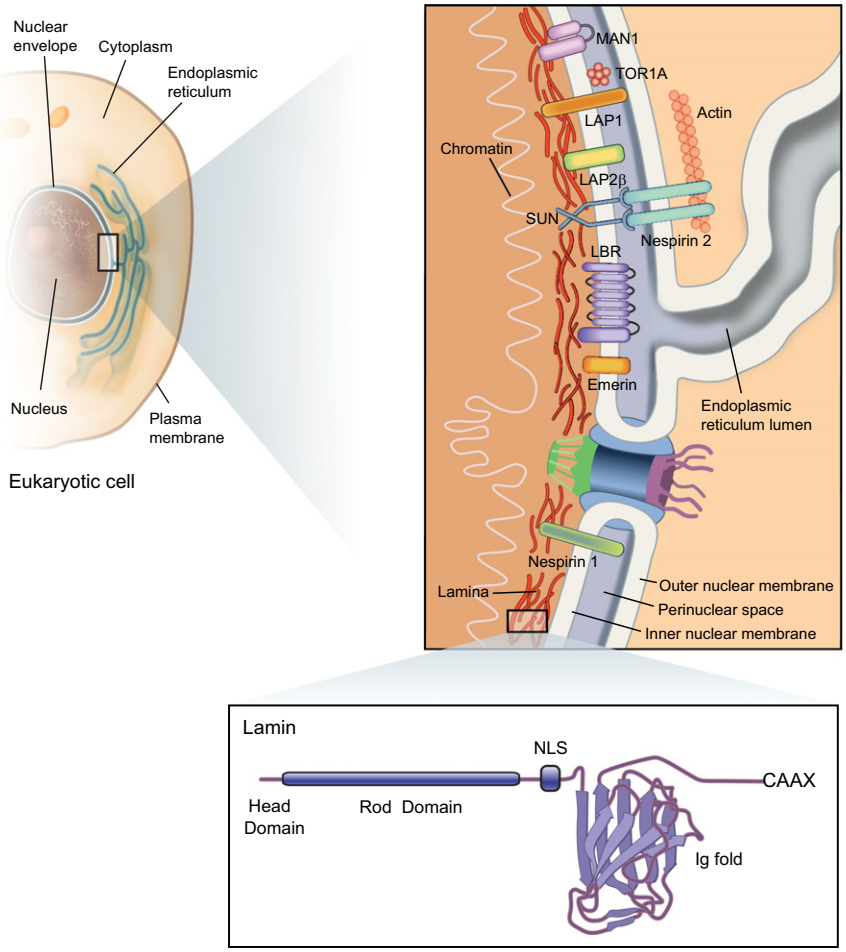

Figure 2. Nuclear Envelope and Nuclear Lamina

The nuclear envelope surrounds the nucleus and is composed the nuclear membranes, nuclear pore complexes, and nuclear lamina. The inner and outer nuclear membranes are separated by the perinuclear space, a continuation of the endoplasmic reticulum lumen. As a result, proteins secreted into the endoplasmic reticulum, such as torsinA (TOR1A), can potentially reach the perinuclear space; a disease-causing torsinA variant preferentially accumulates in the perinuclear space by binding to lamina-associated protein-1. Some proteins, such as large nesprin-2 isoforms, concentrate in the outer nuclear membrane by binding to SUN proteins within the perinuclear space. The nuclear lamina is a meshwork of intermediate filaments on the inner aspect of the inner nuclear membrane and is composed of proteins called lamins. The lamina is associated with integral proteins of the inner nuclear membrane and representative examples—MAN1, lamina-associated polypeptide-1 (LAP1), the SUN protein lamina-associated polypeptide-2β (LAP2 2β), lamin B receptor (LBR), emerin, and a nesprin-1 isoform—are shown. The general structure of a lamin molecule is shown in the lower inset (not to scale). Lamins have α-helical rod domains that are highly conserved among all intermediate filament proteins and are critical for the formation of dimers and higher-ordered filaments. They have head and tail domains that vary in sequence among members of intermediate filament protein family. Within the tail domain, lamins contain a nuclear localization signal (NLS) and an immunoglobulin-like fold (Ig fold). Most lamins (not mammalian lamin C or C2) contain at their carboxyl-termini a CAAX motif that acts as a signal to trigger a series of chemical reactions leading to protein modification by fanesylation and carboxymethylation.

et al., 1986; Goldman et al., 1986) (Figure 2). Though absent from lower eukaryotes such as yeast, the lamina is present in all nucleated cells of higher organisms (Fawcett, 1966; Cohen and Sundeen, 1976; Gerace et al., 1978). Lamins have α-helical central rod domains that are highly conserved among all intermediate filament proteins and head and tail domains that vary in sequence among members of the intermediate filament protein family (Fisher et al., 1986; McKeon et al., 1986). The rod domains are critical for the formation of the dimers and paracrystalline arrays in vitro (Heitlinger et al., 1992). Within the tail domains, lamins contain nuclear localization signals (Fisher et al., 1986; McKeon et al., 1986) and an immunoglobulin-like fold (Dhe-Paganon et al., 2002; Krimm et al., 2002). All the mammalian lamins except for lamin C and lamin C2 contain CAAX motifs at their carboxyl-termini, a signal for farnesylation.

In mammals, three genes encode lamins. The A-type lamins, lamin A and lamin C, arise by alternative RNA splicing from *LMNA*. They share the same first 566 amino acids and differ in their carboxyl-terminal ends. The somatic cell B-type lamins are lamin B1, encoded by *LMNB1*, and lamin B2, encoded by *LMNB2*. Germ-cell-specific isoforms lamin B3 and lamin C2 arise from alternative splicing of transcripts encoded respectively by *LMNB1* and *LMNA*.

Lamin A is synthesized as a precursor called prelamin A. The CAAX motif of prelamin A directs it to become farnesylated on its C-terminal cysteine; the -AAX is then cleaved off by ZMPSTE24, an endoprotease. The carboxyl-terminal cysteine is subsequently carboxymethylated and the farnesylated, carboxymethylated protein is again recognized by ZMPSTE4, which cleaves prelamin A at 15 amino acids "upstream" of the farnesylated cysteine to yield mature lamin A. Only prelamin A undergoes this type of processing; B-type lamins remain farnesylated and carboxymethylated. It remains unclear why B-type lamins are farnesylated but at least one consequence of farnesylation is an enhanced membrane association, either directly or via protein-protein interactions. It is less clear why prelamin A undergoes farnesylation and processing that ultimately leads to removal of the farnesyl group. However, abnormalities in prelamin A processing have detrimental effects that lead to serious disease (discussed below).

Early studies showed that the nuclear lamina of rat liver nuclei contained roughly equivalent amounts of lamin A, "lamin B" (probably mostly lamin B1 and some lamin B2), and lamin C (Gerace et al., 1978). However, observations of differences in lamina "thickness" between various human cell types (Cohen and Sundeen, 1976) indicated that the lamina is not an invariant structure and suggested that differences in protein expression levels and/or stoichiometry may underlie this morphological diversity. In 1987, it was shown that only "lamin B" was present in the lamina of some undifferentiated cell types and that A-type

lamins appeared later in development (Guilly et al., 1987; Stewart and Burke, 1987). Although a comprehensive analysis of multiple cell types and tissues is lacking, data from many different published observations indicate that the different A-type and B-type lamins can be expressed at various stoichiometries in different cells and tissues at various stages of cellular differentiation.

Loss-of-function studies of lamins in model organisms have generally resulted in more profound phenotypes in invertebrates than in mice, likely reflecting the fact that these organisms have fewer lamin isoforms (*C. elegans* has only one) and suggesting a degree of functional overlap between isoforms. Deletion of *lmn-1*, the only *C. elegans* lamin gene, causes early lethality with marked nuclear disorganization, including abnormalities in chromatin organization and chromosome segregation during mitosis (Liu et al., 2000). Deletion of the lamin C homolog in the fly *Drosophila melanogaster* causes a similar, although somewhat less dramatic, early lethal phenotype at the prepupal stage (Schulze et al., 2005). However, loss of *Dm(0)*, which encodes a B-type lamin in *Drosophila*, yields more complex phenotypes. Some *Dm(0)* null flies survive into adulthood, though most die much earlier (Guillemin et al., 2001; Lenz-Böhme et al., 1997; Osouda et al., 2005). Developmental retardation appears to be particularly marked in the central nervous system (CNS) and ovaries, whereas other tissue, such as the ventriculus, is hypertrophic yet normally organized (Osouda et al., 2005). Thus, the *Dm(0)* function does not simply disrupt cell function but may play more specific roles in the differentiation of certain tissues. Similar observations have been made in the development of the tracheal system in *Dm(0)* mutants (Guillemin et al., 2001).

In contrast to findings in invertebrates, mice lacking A-type lamins have apparently normal embryonic development, appearing grossly normal at birth (Sullivan et al., 1999). The postnatal growth of these mice is retarded, however, and they develop abnormalities of cardiac and skeletal muscle. These phenotypes in A-type lamin-deficient mice may result primarily from the loss of lamin C, as mice that selectively lack lamin A appear normal into adulthood (Fong et al., 2006b). Lamin B1 null mice die during early postnatal life and exhibit relatively tissue-specific abnormalities of lung and bone (Vergnes et al., 2004). Interestingly, the bone abnormalities include abnormal overgrowth of cranial structures, a hypertrophic phenotype reminiscent of that seen in *Drosophila Dm(0)* mutants (Osouda et al., 2005).

Nuclear Membrane Proteins

The inner nuclear membrane contains a unique set of transmembrane proteins, many of which interact with the lamina and/or chromatin proteins. Biochemical data from rat liver suggest that approximately 70 transmembrane proteins are relatively concentrated at the inner nuclear membrane (Schirmer et al., 2003). Although there are less systematic data currently available, variable expression of integral inner nuclear membrane proteins likely occurs between differentiated tissues and during cellular differentiation. Genetic deletions in model organisms suggest that proper expression of several integral inner nuclear membrane proteins is essential for normal development. Most studied is MAN1, for which evidence from mice, flies, and frogs support in vitro experiments implicating this protein in transforming growth factor-β signaling. This is consistent with disease phenotypes of patients with mutations in *LEMD3* encoding MAN1 (see below). MAN1-deficient mice die during embryogenesis as a result of abnormal yolk-sac vascularization (Ishimura et al., 2006; Cohen et al., 2007) and exhibit abnormal heart morphogenesis resulting from aberrant expression of left-side-specific genes responsible for left-right asymmetry (Ishimura et al., 2008). Both of these defects have been linked to enhanced transforming growth factor-β signaling. Similarly, tissue-specific defects resulting from deletion of the MAN1 homolog in *Drosophila* (Pinto et al., 2008) and abnormalities caused by overexpression or knockdown of the *Xenopus* MAN1 homolog in embryos (Osada et al., 2003; Raju et al., 2003) appear to result from alterations in signaling by transforming growth factor-β family members.

Spontaneous mutations at the mouse ichthyosis locus, shown by Shultz et al. (2003) to lead to loss of expression of the inner nuclear membrane protein lamin B receptor, lead to hair and skin abnormalities as well as clumping of heterochromatin in the nuclei of neutrophils, lymphocytes, and other cells. Mice with a gene trap insertion into the *Lbr* locus have a similar phenotype, and both lines of LBR-deficient mice demonstrate that this protein is essential for the morphological maturation of neutrophils (Cohen et al., 2008). This is consistent with the observation that heterozygous mutations in human *LBR* cause the Pelger-Huët anomaly (see below). Mice with deletions of the X chromosome gene encoding emerin, another integral protein of the inner nuclear membrane, are fertile and have normal lifespans with only very subtle abnormalities of striated muscle (Melcon et al., 2006; Ozawa et al., 2006), although loss of emerin in humans causes significant cardiac and skeletal muscle disease (see below). Deletions of genes encoding the inner nuclear membrane SUN proteins, which bind to nesprins in the outer nuclear membrane as part of the nucleo-cytoskeletal LINC complex, result in defects mostly involving proper nuclear positioning and cell migration (reviewed by Burke and Roux, 2009).

Positional Cloning Brings a New Perspective to the Nuclear Envelope

Following the discovery by positional cloning that mutations in the *EDM* gene cause X-linked Emery-Dreifuss muscular dystrophy (Bione et al., 1994), it came as a surprise when its gene product, emerin, was localized to the nuclear envelope (Manilal et al., 1996; Nagano et al., 1996). Even more surprising was the identification by Bonne et al. (1999), using positional cloning, that mutations in *LMNA*, the gene that encodes the long-studied A-type lamins, cause autosomal dominant Emery-Dreifuss muscular dystrophy (a phenocopy of the X-linked form). Hence, in contrast to the severe, potentially lethal phenotypes most cell biologists might have suspected, defects in widely expressed nuclear envelope proteins were shown to have tissue-selective effects that do not manifest until well after birth, in some cases only appearing during adulthood. These discoveries challenged existing concepts of nuclear envelope function and have led to new insights into the function of this organelle, especially with regard to development and disease. It is now clear that several Mendelian diseases result from mutations in genes encoding widely-expressed components of the nuclear lamina, nuclear membranes, and nuclear pore complexes and that many of these manifest as tissue-selective disorders (Table 1).

Table 1. Disorders Caused by Mutations in Genes Encoding Nuclear Envelope Proteins

Nuclear Envelope Component	Gene	Protein(s)	Expression	Major Protein Function	Phenotype (Main Affected Tissues)
Lamina	*LMNA*	LaminA, LaminC	most differentiated somatic cells	structural support of nucleus; implicated in DNA synthesis and transcription	(1) cardiomyopathy sometimes with muscular dystrophy (cardiac and skeletal muscle); (2) partial lipodystrophy (adipose); (3) peripheral neuropathy (peripheral nerve); (4) progeroid features (early aging affecting several tissues including skin, adipose, arteries); and (5) mandibuloacryl dysplasia (bone, adipose, some progeroid features)
	LMNB1	Lamin B1	all or most somatic cells	as above	leukodystophy (CNS glial cell)
	LMNB2	Lamin B2	as above	as above	possible partial lipodystrophy (adipose)
	ZMPSTE24	ZMPSTE24	as above	processing of prelamin A	progeroid features and restrictive dermopathy (skin and bone)
Nuclear membranes and perinuclear space	*EDM*	Emerin	as above	binds lamins and other proteins	cardiomyopathy with muscular dystrophy (cardiac and skeletal muscle)
	LBR	Lamin B receptor	as above	binds B-type lamins, DNA, and heterochromatin protein 1; sterol reductase	(1) Pelger-Huët anomaly (heterozygous; neutrophils) and (2) Greenberg skeletal dysplasia (homozygous; multi-systemic developmental abnormalities most prominently affecting bone that causes neonatal lethality)
	LEMD3	MAN1	as above	binds rSmads, antagonizing TGF-β signaling	sclerosing bone dysplasia (bone and sometimes also skin)
	SYNE1	Nesprin-1	as above	component of LINC complex that connects nucleus to cytoplasmic cytoskeleton	cerebellar ataxia (CNS neurons)
	TOR1A	TorsinA	as above	AAA+ ATPase of ER and perinuclear space; binds lamina-associated polypeptide 1	DYT1 dystonia (CNS neurons)
	AAAS	Aladin	as above	nuclear pore-associated	triple-A syndrome (lower esophageal sphinter, adrenal gland, lacrimal gland)
Nuclear pore complex	*NUP155*	Nup155	as above	nucleocytoplasmic transport	atrial fibrillation (heart)
	NUP62	Nup62	as above	nucleocytoplasmic transport	infantile striatal necrosis (CNS)
	RANBP2	RanBP2	as above	nucleocytoplasmic transport	acute necrotizing encephalopathy (CNS)

The Fascinating Case of LMNA

More than a dozen differently named clinical conditions (''laminopathies'') have been linked to mutations in *LMNA*. These clinical conditions can be grouped into phenotypes selectively involving striated muscle, adipose tissue, peripheral nerve, or multiple systems (Figure 3). Most inherited *LMNA* mutations cause disorders that selectively affect striated muscle, with or without tendon involvement. The laminopathies that involve striated muscle are almost all dominantly inherited and always affect the heart, which appears clinically as a dilated cardiomyopathy with conduction system defects. Skeletal muscle involvement is sometimes in a classical Emery-Dreifuss distribution (Figure 3) but can be variable or absent even for the same mutation, indicating the potential involvement of modifier genes. The mutations that cause myopathy syndromes are mostly missense or small in-frame deletions, which lead to expression of variant proteins, or to splice site, truncation, or promoter mutations that result in decreased levels of A-type lamins. Loss-of-function of A-type lamins may underlie striated muscle disease, as *Lmna* null mice develop abnormalities of cardiac and skeletal muscle reminiscent of those seen in human subjects (Sullivan et al., 1999). However, in humans, this loss of function may result as a consequence of some type of ''dominant interference'' mechanisms in the cases in which a variant lamin is expressed, as demonstrated by the development of severe heart damage in transgenic mice overexpressing a lamin A variant

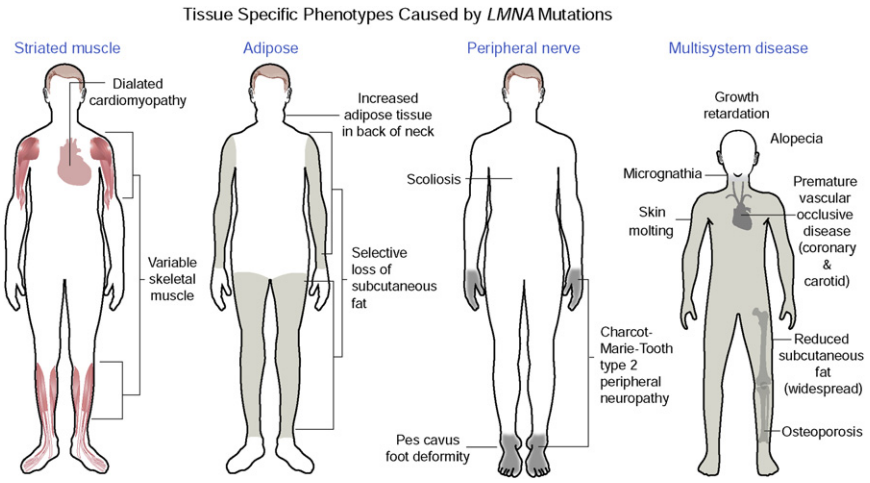

Figure 3. *LMNA* Mutations Cause Distinct Tissue-Specific Phenotypes

Different *LMNA* mutations selectively affect striated muscle, adipose, peripheral nerve, or multiple systems. The majority of autosomal dominant mutations cause dilated cardiomyopathy with variable skeletal muscle involvement. The diagram shows the classical Emery-Dreifuss muscular dystrophy scapulohumeral-peroneal distribution of skeletal muscle involvement, in which there is usually concurrent tendon contractures. However, the same *LMNA* mutations can result in cardiomyopathy with minimal to no skeletal muscle disease or involvement in a limb-girdle distribution. Other autosomal dominant missense mutations in *LMNA,* mostly those leading to a change in the surface charge of the immunoglobulin fold in lamins A and C, cause Dunnigan-type partial lipodystrophy, which has selective loss of subcutaneous fat from the extremities, excessive fat accumulation in the neck and face, and in most cases, the subsequent development of insulin resistance and diabetes mellitus. The autosomal recessive R298C *LMNA* mutation causes a Charcot-Marie-Tooth type 2 peripheral neuropathy, characterized by a stocking-glove sensory neuropathy, an associated pes cavus foot deformity, and additional variable features such as scoliosis. The de novo dominant *LMNA* G608G mutation causes the multisystem disease HGPS, with progeroid features including growth retardation, micrognathia (small jaw), reduced subcutaneous fat, alopecia, osteoporosis, skin mottling, and premature vascular occlusive disease. Other rare *LMNA* mutations also cause progeriod syndromes with some of the same features. The autosomal recessive *LMNA* R527H mutation causes mandibuloacryl dysplasia, a disorder with a combination of progeroid features and partial lipodystrophy.

that occurs in patients with Emery-Dreifuss muscular dystrophy (Wang et al., 2006).

Dominantly inherited missense mutations, most frequently those that change the surface charge of the immunoglobulin fold in the tail domain of lamins A and C, cause Dunnigan-type partial lipodystrophy, characterized by the selective loss of peripheral subcutaneous fat around the time of puberty and, in most cases, the subsequent development of insulin resistance and diabetes mellitus (Cao and Hegele, 2000; Shackleton et al., 2000; Speckman et al., 2000; Dhe-Paganon et al., 2002; Krimm et al., 2002). Missense mutations that alter other regions of A-type lamins may cause the same condition or slightly different forms of partial lipodystrophy. *Lmna* null mice do not develop lipodystrophy (Cutler et al., 2002), whereas overexpression of lamin A blocks adipocyte differentiation in vitro (Boguslavsky et al., 2006), indicating that lipodystrophy-causing mutations may act via a gain-of-function mechanism. Interestingly, a recessively inherited missense mutation (R527H) in the immunoglobulin fold causes mandibuloacryl dysplasia, a disorder characterized by partial lipodystrophy, progeroid features, mandibular hypoplasia, and associated congenital bone abnormalities, further emphasizing the functional importance of this *LMNA* domain (Novelli et al., 2002).

Alterations in A-type lamins also lead to a selective disorder of peripheral nerve (De Sandre-Giovannoli et al., 2002). A recessively inherited missense mutation (R298C) in the region of *LMNA* encoding the rod domain of A-type lamins causes an axonal neuropathy affecting peripheral nerves (classified as Charcot-Marie-Tooth disease type 2B1). The sciatic nerves of *Lmna* null mice show reduced axon density, axonal enlargement, and the presence of unmyelinated axons (De Sandre-Giovannoli et al., 2002), features similar to those seen in human patients and consistent with the possibility that the R298C mutation may impair some aspect of *LMNA* function.

Although there have been case reports of *LMNA* mutations leading to various combinations of abnormalities between striated muscle, fat, and peripheral nerve, for the most part, most different *LMNA* mutations cause these different tissue-selective disease phenotypes with minimal overlap. However, one group of disorders caused by *LMNA* mutations, the progerias, is clearly multisystemic. Hutchinson-Gilford progeria syndrome (HGPS) is a rare but fascinating disorder that has long captured the imagination of physicians and the lay public alike. Children with HGPS appear normal at birth but by the first year of life show growth retardation, micrognathia (small jaw), reduced subcutaneous fat, alopecia, osteoporosis, and skin mottling. They subsequently develop premature vascular occlusive disease, with most dying in the second decade from complications of coronary artery or cerebrovascular disease. These features have led to the notion that HGPS is a disorder of accelerated or premature aging, but some tissues that are commonly affected during physiological aging in later decades, such as the brain, are not affected in children with this disorder.

Most cases of HGPS are caused by a dominant de novo point mutation (G608G) that creates a novel splice donor site within exon 11 of *LMNA*, causing an in-frame deletion of 150 base pairs from this exon (Eriksson et al., 2003; De Sandre-Giovannoli et al., 2003). Exons 11 and 12 of *LMNA* encode amino acids specific to prelamin A, the precursor of lamin A, and not lamin C. Therefore, the G608G HGPS-causing mutation causes an in-frame deletion of 50 amino acids of near the carboxyl-terminus of prelamin A that includes the ZMPSTE24 cleavage site (see discussion of prelamin A processing in *Nuclear Lamina* section above). The mutation therefore leads to the production of a truncated, permanently farnesylated form of prelamin A, termed "progerin."

Several lines of evidence suggest strongly that accumulation of farnesylated progerin contributes significantly to the progeroid phenotype of HGPS. *Zmpste24* null mice accumulate permanently farnesylated prelamin A and exhibit a progeroid phenotype (Bergo et al., 2002; Pendás et al., 2002). Similarly, loss-of-function mutations in *ZMPSTE24* cause a neonatal lethal progeria-related syndrome in humans, termed restrictive

dermopathy (Navarro et al., 2005). Moreover, blocking protein farnesylation partially ameliorates the progeroid phenotype in both *Zmpste24* null mice that accumulate farnesylated prelamin A and *LMNA* knockin mice that express progerin (Fong et al., 2006a; Yang et al., 2006). The progeroid phenotype of *Zmpste24* null mice also depends on the gene dosage of prelamin A (Fong et al., 2004). A study exploring the disease-causing features of progerin demonstrated, however, that it has farnesylation-dependent and farnesylation-independent toxicities (Yang et al., 2008). These authors generated and compared two lines of progerin-expressing mice, one of which had an additional mutation preventing farnesylation. The mice expressing nonfarnesylated progerin still developed progeroid features, though the phenotype was milder than that of the line expressing farnesylated progerin. Atypical progeriod disorders are also caused by *LMNA* missense mutations that do not lead to accumulation of progerin or farnesylated prelamin A, and mandibuloacryl dysplasia, caused by the *LMNA* R527H mutation, has progeroid features, further confounding our understanding of the pathogenesis these enigmatic disorders.

Nuclear Envelope-Related Diseases That Are Phenocopies of LMNA Myopathy

As described above, the first identified nuclear envelopathy was X-linked Emery-Dreifuss muscular dystrophy, an identical disease to that caused by some of the dominantly inherited *LMNA* mutations discussed above. X-linked Emery-Dreifuss muscular dystrophy is caused by mutations in the *EDM* gene encoding emerin (Bione et al., 1994), a single-pass transmembrane protein that normally concentrates at the inner nuclear membrane by binding to lamin A via its nucleoplasmic domain. Most of these are nonsense mutations that cause a loss of emerin from all cell types. In fibroblasts from *Lmna* null mice, emerin redistributes from the inner nuclear membrane to the endoplasmic reticulum, and a similar effect is observed when A-type lamin variants that cause myopathy are overexpressed in cultured cell lines (Sullivan et al., 1999; Östlund et al., 2001; Raharjo et al., 2001). These data suggest that the loss of inner nuclear membrane-localized emerin function is an important event in most, if not all, causes of Emery-Dreifuss muscular dystrophy. Limited data suggest that mutations or polymorphisms in the genes encoding lamina-associated polypeptide 2 and nesprins, proteins that interact directly or indirectly with A-type lamins, may also be associated with disease phenotypes affecting striated muscle (Taylor et al., 2005; Zhang et al., 2007). A-type lamins, nesprins, and possibly emerin are components of the LINC complex that connects the nuclear envelope to cytoskeletal networks (reviewed by Burke and Roux, 2009) suggesting that the integrity of nucleocytoplasmic connections mediated by this complex may be particularly important in striated muscle cells.

CNS-Specific Nuclear Envelopathies

While the disorders caused by *LMNA* mutations spare the brain, mutations in other genes encoding nuclear envelope proteins cause diseases that selectively affect the CNS. Duplication of the ubiquitously expressed *LMNB1* gene that encodes lamin B1 causes dominantly inherited adult-onset leukodystrophy, a disease characterized by a selective yet widespread loss of CNS myelin (Padiath et al., 2006). In humans, *LMNB1* duplication causes approximately 1.5-fold increase in lamin B1 levels (Padiath et al., 2006), and overexpression of lamin B1 leads to the premature arrest of oligodendrocyte differentiation, alterations in other nuclear envelope proteins and chromatin organization, and reduced transcription of myelin-related genes (Lin and Fu, 2009).

Deletion mutations in *SYNE1* encoding nesprin-1 cause a recessively inherited cerebellar ataxia (Gros-Louis et al., 2007). However, it is not clear if the disease-causing mutations specifically affect nesprin-1 isoforms localized to the inner nuclear membrane, the LINC complex or elsewhere. One report so far suggests that, depending upon the nature of the mutation in this gene with many exons and alternatively spliced RNAs, more extensive, multi-systemic disease can result (Attali et al., 2009). Another CNS selective nuclear envelopathy is DYT1 dystonia, a developmental disorder of childhood characterized by sustained abnormal involuntary movements that cause twisting and turning of the involved body part. DYT1 dystonia is caused by a dominantly inherited in-frame single amino acid deletion the *TOR1A* gene that encodes the AAA-ATPase torsinA (Ozelius et al., 1997). TorsinA is largely localized to the endoplasmic reticulum peripheral to the nuclear envelope but the DYT1 mutation causes it to concentrate abnormally in the perinuclear space of the nuclear envelope (Gonzalez-Alegre and Paulson, 2004; Goodchild and Dauer, 2004; Naismith et al., 2004). TorsinA deficient or disease mutation knock in mice are phenocopies of each other: both exhibit morphological abnormalities of nuclear membranes selectively in neurons (Goodchild et al., 2005). These data suggest that neurons have a unique requirement for nuclear envelope-localized torsinA function and suggest that the DYT1 dystonia mutation impairs this activity. TorsinA interacts with the nuclear envelope proteins lamina-associated polypeptide-1 (Goodchild and Dauer, 2005) and nesprin-3 (Nery et al., 2008), possibly influencing the structure or function of the LINC complex. The mechanisms underlying the CNS specificity of nesprin-1-related cerebellar ataxia or DYT1 dystonia are not understood.

Other Nuclear Envelopathies

Mutations in other widely expressed nuclear envelope proteins also cause disorders that are relatively tissue specific. Polymorphisms or mutations in the gene *LMNB2*, which encodes lamin B2, appear to predispose patients to develop an acquired lipodystrophy (Hegele et al., 2006). Dominantly inherited mutations in *LBR*, which encodes the lamin B receptor that binds to B-type lamins and chromatin, cause Pelger-Huët anomaly (Hoffmann et al., 2002). Pelger-Huët anomaly is a clinically silent alteration of nuclear shape in which the nuclei of blood neutrophils are bilobed rather than the normal multilobular morphology. Homozygous mutations in *LBR* lead to the perinatal lethal syndrome Greenberg's skeletal dysplasia. This syndrome affects bone and several other organ systems and may be related to loss of the sterol reductase activity of lamin B receptor or to the absence of its lamin or chromatin binding features (Waterham et al., 2003).

Nucleoporinopathies

Approximately 30 different proteins, including those known as nucleoporins, comprise the nuclear pore complex, the sole site

of nucleocytoplasmic transport (Hetzer and Wente, 2009). Although pore complex proteins are assumed to be ubiquitously expressed, recent data suggest that this is not always the case. Moreover, as reviewed above, a growing body of literature is implicating nuclear pore proteins in additional cellular functions, most notably in mitosis. These new discoveries may in part account for the varied group of diseases that result from mutations in nuclear pore complex proteins. Achalasia-Addisonianism-Alacrima syndrome, also known as triple-A syndrome, is a recessively inherited disorder characterized by adrenal insufficiency, dysfunction of the lower esophageal sphincter that interfers with normal swallowing (achalasia), and dry eyes (alacrima). Triple-A syndrome is caused by loss-of-function mutations in the *AAAS* gene that encodes a WD-repeat protein called aladin (Tullio-Pelet et al., 2000). Aladin is a component of the nuclear pore complex, but the triple-A mutation prevents pore localization (Cronshaw et al., 2002; Cronshaw and Matunis, 2003). However, no studies have determined whether the mislocalization of aladin causes abnormal nuclear pore transport or whether, similar to other pore proteins, aladin has functions distinct from its role at the nuclear pore.

More recently, a recessively inherited missense mutation in the nucleoporin gene *NUP155* was found to cosegregate with atrial fibrillation, which causes sudden death; heterozygous null *Nup*155 mice also develop atrial arrhythmias (Zhang et al., 2008). Loss of NUP155 function appears to disrupt nuclear pore function (Zhang et al., 2008), and in contrast to most nuclear envelopathies, the relatively increased expression of NUP155 in the heart appears to at least partly explain the preferential involvement of cardiac tissue. Lastly, two other nucleoporinopathies manifest as clinically related CNS disorders. A recessively inherited missense mutation in the nucleoporin gene *NUP62* causes infantile bilateral striatal necrosis (Basel-Vanagaite et al., 2006), whereas a dominantly inherited missense mutation in *RanBP2*, encoding another nucleoporin, leads to susceptibility to infection-triggered acute necrotizing encephalopathy (Neilson et al., 2009). While these are distinct disorders, they both feature the acute development of bilateral necrotic lesions of deep brain structures. It is also interesting that acute necrotizing encephalopathy is triggered by viral or other infections, given that $Nup96^{+/-}$ mice also have defects in innate and adaptive immunity (Faria et al., 2006). These intriguing reports suggest that nuclear pore complex composition may not be invariant during development and in different tissues and that certain proteins have tissue-specific roles, possibly in mediating nucleocyoplasmic transport of particular cargoes.

Beyond the Barrier Function of the Nuclear Envelope

The data from model organisms and human subjects with Mendelian diseases convincingly demonstrate that the nuclear envelope functions as much more than a simple barrier separating the nuclear and cytoplasmic compartments. This has led to the hypothesis that, in addition to its barrier function, the nuclear envelope is a node that integrates important signals in developing and mature tissue and that the disruption of nuclear-envelope-localized signaling contributes to a diverse array of human diseases, perhaps even normal aging. These "signaling" functions are likely to be diverse, ranging from the regulation of "classical" signal transduction pathways, to integration of cellular mechanical events and to the control of the nucleocytoplasmic transport of specialized cargoes.

Studies of the inner nuclear membrane protein MAN1 illustrate how the nuclear envelope can participate in the regulation of a classical signaling pathway. MAN1 has an amino-terminal nucleoplasmic domain, two transmembrane segments, and a nucleoplasmic carboxyl-terminal domain. The carboxyl-terminal domain of mammalian MAN1 binds to rSmads, antagonizing cellular responses to transforming growth factor-β and bone morphogenic protein (Hellemans et al., 2004; Lin et al., 2005; Pan et al., 2005). Inhibition of transforming growth factor-β signaling by MAN1 has been confirmed in knockout mice deficient for the protein (Ishimura et al., 2006; Cohen et al., 2007). Consistent with these findings, human subjects with heterozygous loss of function mutation in the gene encoding MAN1 exhibit bone and skin abnormalities, potentially because of enhanced sensitivity of these tissues to transforming growth factor-β or bone morphogenic protein (Hellemans et al., 2004). Transforming growth factor-β superfamily signaling is regulated at multiple steps, and the fact that selective abnormalities of bone and skin result from the loss of MAN1 function indicates that it is a particularly relevant negative regulator of signaling in these tissues during postembryonic life. Evidence suggests that A-type lamins may also play a role in controlling transforming growth factor-β signaling by affecting the activities of downstream nuclear phosphatases (van Berlo et al., 2005). Redundant steps in the regulation of signal transduction pathways that are variable in different cell types could potentially explain tissue-selective phenotypes in other diseases associated with nuclear envelope alterations.

Abnormalities in A-type lamins have been shown to impact on the activities of other signal transduction pathways. Expression of progerin, the truncated prelamin A in HGPS, activates Notch signaling, promoting the differentiation of mesenchymal stem cells down an osteogenic as opposed to an adipogenic fate (Scaffidi and Misteli, 2008). Similarly, $Zmpste24^{-/-}$ mice that accumulate unprocessed, farnesylated prelamin A exhibit abnormalities in the proliferative capacity of epidermal stem cells and altered signaling, including that through the Wnt pathway (Espada et al., 2008). A-type lamins bind to retinoblastoma protein (Mancini et al., 1994; Ozaki et al., 1994), likely in complex with the nucleoplasmic protein lamina-associated polypeptide-2α (Pekovic et al., 2007). In cells lacking A-type lamins, lamina-associated polypeptide-2α is mislocalized within nuclear aggregates and this occurs concurrently with cell cycle arrest and accumulation of retinoblastoma protein within nuclear speckles (Pekovic et al., 2007). Loss of emerin also disrupts retinoblastoma protein/E2F and MyoD pathways during muscle regeneration (Melcon et al., 2006). These signaling pathways play critical roles in controlling proliferation, fate determination and other aspects of stem cell biology, demonstrating a possible function of the nuclear lamina in cell differentiation during development as well as the maintenance of somatic tissues.

Apart from these "classical" signal transduction pathways, several lines of evidence suggest that the nuclear envelope plays an important role in the modulation of mechanical stress-induced signaling pathways. Fibroblasts from mice lacking A-type lamins exhibit altered nuclear morphology and defective nuclear mechanics and abnormally activate transcriptional

responses in response to mechanical strain (Lammerding et al., 2004), and similar abnormalities are present in cells from human subjects with HGPS that express progerin (Verstraeten et al., 2008). Abnormalities of stress-related signaling have also been observed in cardiac tissue from *Lmna* knockin mice that carry an Emery-Dreifuss muscular dystrophy missense mutation (Muchir et al., 2007). In cardiac cells, mechanical stress activates the ERK and JNK branches of the MAP kinase pathway. In $Lmna^{H222P/H222P}$ mice, these pathways appear to be abnormally activated in heart and, to a lesser extent, skeletal muscle, suggesting that only cells continually exposed to mechanical strain have abnormal activation. Long-term superactivation of ERK and JNK are detrimental to normal heart functioning and systemic treatment with an inhibitor of ERK signaling prevents or delays the onset of cardiomyopathy in $Lmna^{H222P/H222P}$ mice (Muchir et al., 2009), potentially linking these aberrant signaling events to a clinically relevant disease phenotype. Defects in protein interactions leading to mechanical instability could directly contribute to cellular damage, independent of resultant alterations in signaling pathways, particularly in cells under constant mechanical stress, such as myocytes. Nonetheless, these data illustrate how an underlying abnormality of nuclear envelope structure or function can be amplified by the unique features of a particular cell type, a scenario that may contribute to the tissue-selective phenotypes characteristic of nuclear envelopathies.

One can imagine similarly variable responses to other stressors, such as the complex, coordinated events that occur between the nucleus and cytoskeleton during major cell migratory events that take place during embryonic development. As noted above and reviewed elsewhere in this issue by Burke, the nucleus is connected to cytoskeletal elements via the LINC complex. The LINC complex appears to play a critical role in nuclear positioning and movement, events that are critical for proper cell migration. Indeed, fibroblasts lacking nesprin-2-giant or A-type lamins have abnormal nuclear movement and cell migration (Lee et al., 2007; Lüke et al., 2008). Well-coordinated nuclear movements appear particularly important during CNS development, where they are important in both neurogenesis and neuronal migration. For example, as neural precursor cells migrate into developing neocortex, centrosomes move continuously and in advance of nuclei, which follow by leaps rather than by smooth, gradual transitions (Tsai et al., 2007). Disruption of the nuclear envelope or variations in connections to cytoskeletal elements, either via the LINC complex or other attachments, could disrupt these processes, causing relatively selective effects on cell types that heavily utilize these processes. Fibroblasts lacking torsinA, the protein affected in the CNS selective nuclear envelopathy, also exhibit abnormalities in nuclear movement and cell migration (Nery et al., 2008), raising the possibility that abnormalities of neuronal migration could contribute to the pathogenesis of this neurodevelopmental disorder.

The nuclear pore complex itself, which controls signaling between the cytosol and nucleus through its classical transport function, has similarly emerged as a highly complex machine that modulates many aspects of cellular behavior through a range of increasingly understood nonclassical functions. The pore complex is intimately involved in the regulation of gene action by controlling the passage of transcription factors in and mRNA out of the nucleus. As the lamina is associated with nuclear pore complexes (Gerace et al., 1978), alterations in the lamins or associated integral inner nuclear membrane proteins may affect specific nuclear pore-related processes. The lamin-binding inner nuclear membrane protein emerin, which is not expressed in most cases of X-linked Emery-Dreifuss muscular dystrophy, appears to stimulate the export of β-catenin, and loss of emerin leads to increased nuclear accumulation of this transcription coactivator (Markiewicz et al., 2006). There is also increasing evidence to suggest that the "FG repeat" motif found in multiple nucleoporins can function as direct transcriptional activators, even at intranuclear sites distant from the nuclear pore (Wang et al., 2007). Nucleoporins have also been localized to the kinetochore and at microtubules and have been implicated as attachment sites for nucleocytoskeletal connections (Zuccolo et al., 2007). These varied functions likely contribute to the unexpected diversity of phenotypes that result from mutations in nuclear pore components, both in model organisms and human disease.

Future Perspectives and Directions

Apart from the great progress made in understanding nucleocytoplasmic transport through the nuclear pore, it has been tremendously challenging to identify and dissect the specific biological processes that occur at the nuclear envelope. Indeed, a relatively complete accounting of the mammalian inner nuclear membrane proteome has only fairly recently been obtained in only one tissue, and the state of knowledge of nuclear envelope-linked functions is exemplified by the "Nuclear Envelope Transmembrane (NET)" nomenclature used to identify these proteins (Schirmer et al., 2003). Nevertheless, the continuing characterization of nuclear envelope proteins, for example, the nesprins, is leading to important new insights into nuclear envelope organization and function. Importantly, recent years have witnessed tremendous advances in linking human disease to mutations in genes encoding nuclear envelope proteins. These discoveries, which may be viewed as "nature's experiments," are valuable because they connect (often surprisingly) whole organism phenotypes to nuclear envelope proteins and, thus, form the basis for future mechanistic studies aimed at linking these proteins to biological functions.

Some of the striking tissue selectivity observed in human nuclear envelopathies and related model organisms may simply be due to differences in the developmental expression patterns in different cell and tissues types. However, only a few small studies have characterized the developmental expression patterns of individual nuclear envelope proteins in various cells and tissues, the most comprehensive being an analysis of the onset of A-type lamin expression during early mouse development (Röber et al., 1989). A comprehensive and systemic analysis of the nuclear envelope proteome in different mammalian tissues at different developmental stages is clearly needed. This information would likely provide insight into some of the striking phenotypes that result from altering the function of nuclear envelope proteins and would be a valuable resource for the research community. A similar analysis, performed in human tissues from patients with nuclear envelopathies or mouse models of these diseases, would enable investigators to correlate disease and developmental phenotypes with alterations in protein expression patterns.

Another current limitation of our understanding of the functions of nuclear envelope proteins in different vertebrate tissues is the fact that many of these proteins have essential functions during embryogenesis, leading to the frequent occurrence of embryonic lethality in mouse mutants. For example, *Lemd3* null mice that do not express MAN1 die at embryonic day 10.5 secondary to abnormal yolk sac vasculogenesis, preventing the study of this protein in mature bone. This issue is of considerable interest because of occurrence of sclerosing bone dysplasias in patients with dominantly inherited mutations in the homologous gene in humans. Thus, the generation and characterization of mice with conditional loss-of-function alleles for nuclear envelope proteins is needed to explore the role of these proteins in mature tissues. Importantly, the European Conditional Mouse Mutagenesis Project (EUCOMM; http://www.eucomm.org/) is currently generating a number of such mice, which are freely available to academic researchers.

Considerable attention has been given to the abnormal gross nuclear envelope architecture that occurs in cells with mutations in genes encoding nuclear envelope proteins and from subjects with ''laminopathies.'' Indeed, altered nuclear morphology has been considered a virtually defining feature of laminopathies. The abnormal nuclear morphology, which includes ''blebbing'' and increased lobulation of the nuclear envelope, appears to be related to disease pathogenesis, as interventions that ameliorate physiological phenotypes in mice also affect the reversal of nuclear shape alterations in cultured cells. For example, administration of a farnesyltransferase inhibitor to a mouse model of HGPS improves body weight curves, reduces bone abnormalities, and also reverses the abnormalities in nuclear morphology in fibroblasts cultured from these animals (Yang et al., 2005, 2006). However, such correlations do not resolve whether the observed abnormal nuclear envelope abnormalities are actually responsible for a specific cellular phenotype or whether this is a correlation without causation. Future studies must go beyond correlating abnormalities in nuclear envelope morphology with phenotypes. They must instead attempt to explain whether and how altered nuclear morphology contributes to pathogenic mechanisms, such as abnormal signal transduction, nucleocytoplasmic transport, or cell stability. In particular, the potential effects of altered nuclear structure on nucleocytoplasmic transport have received little attention to date. Studies that link the effects of altered nuclear morphology to pathogenic mechanisms will be of value far beyond the relatively rare inherited nuclear envelopathies, as the disruption of nuclear envelope morphology is also implicated as an important pathogenic events in cancer as well as aging. Thus, structure-function of the nuclear envelope are likely to yield a number of insights that are both fundamentally important to the study of both cell physiology and human disease.

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