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Broken nuclei – lamins, nuclear mechanics and disease

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Abstract

Mutations in lamins, which are ubiquitous nuclear intermediate filaments, lead to a variety of disorders, including muscular dystrophy and dilated cardiomyopathy. Lamins provide nuclear stability, help connect the nucleus to the cytoskeleton, and can modulate chromatin organization and gene expression. Nonetheless, the diverse functions of lamins remain incompletely understood. Here, we focus on the role of lamins on nuclear mechanics and its implication in human diseases. Recent findings suggest that lamin mutations can decrease nuclear stability, increase nuclear fragility, and disturb mechanotransduction signaling, possibly explaining the muscle-specific defects in many laminopathies. At the same time, altered lamin expression has been reported in many cancers, where the resulting increased nuclear deformability could enhance the ability of cells to transit tight interstitial spaces, promoting metastasis.

Keywords

Protein assembly/structure; cell mechanics; gene regulation; cytoskeleton; laminopathy

Lamins and disease

Since the discovery in 1999 that mutations in the nuclear envelope proteins lamin A/C cause Emery-Dreifuss muscular dystrophy (EDMD) [1], lamins and lamin-associated proteins have garnered increasing interest in the scientific and medical community, resulting in the discovery of over 450 disease-associated lamin mutations to date (see <http://www.umd.be/LMNA/>). These ‘laminopathies’ include EDMD, dilated cardiomyopathy (DCM), Dunnigan-type familial partial lipodystrophy (FPLD), and Hutchinson-Gilford progeria syndrome (HGPS), a premature aging disorder [2]. Given that lamins A/C are expressed in nearly all cells and tissues, the high degree of tissue-specificity and the broad range of diseases caused by different mutations in the same gene are quite perplexing. Despite extensive research efforts, the molecular mechanisms underlying laminopathies remain to be fully explained.

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In addition to providing structural support to the nucleus, lamins also contribute to nucleo-cytoskeletal coupling, chromatin organization, epigenetic modifications, DNA replication, transcriptional regulation and repair, and responses to oxidative stress [2]. In this review, we focus on the mechanical aspects of lamin functions, including governing nuclear deformability and fragility, physically connecting the nucleus and the cytoskeleton, and contributing to mechanotransduction signaling, i.e., the cells' ability to respond to mechanical stimuli. These functions could be particularly relevant to muscular dystrophies and cardiomyopathies caused by mutations in lamins A/C. At the same time, striking new reports suggest that nuclear deformability, which is modulated by the expression of specific lamin isoforms, can constitute a rate-limiting factor in the ability of cells to pass through micrometer-sized constrictions in three-dimensional (3-D) environments [3,4], which has important implications in cancer progression, immune cell function, and development.

Lamins – primary components of the nuclear lamina

The lamina is a dense protein meshwork underlying the inner nuclear membrane that is composed of lamins and lamina-associated proteins. In somatic cells, the predominant lamins are lamins A and C (referred to as A-type lamins), resulting from alternative splicing of the *LMNA* gene, and the B-type lamins, lamin B1 and B2. While most differentiated cells express at least one A-type lamin, embryonic stem cells, the lower layer of epidermis [5], and the central nervous system [6] produce little to no lamin A. These latter findings may explain why the central nervous system is typically spared in diseases arising from *LMNA* mutations. In contrast, striated muscles and many mesenchymal cells have particularly high levels of A-type lamins, which may contribute to their prominent involvement in many laminopathies.

Unlike A-type lamins, B-type lamins are expressed by all cells throughout development. B-type lamins were previously considered essential for cell viability, based on knockdown studies in human cells [7] and *C. elegans* [8], but recent studies indicate that at least in mice, B-type lamins are dispensable in many cell types, including embryonic stem cells [9,10] and skin cells [11]. Nonetheless, lamins B1 and B2 are necessary for organogenesis [9], and mice lacking lamins B1 and/or B2 die shortly after birth with severe defects in neuronal development and migration [12]. These contrasting findings may reflect changes in experimental conditions (acute knockdown in the human and *C. elegans* cells versus selection of stable lamin B-deficient embryonic stem cells), or they may result from cell- or species-specific differences. Regardless, the findings consistently point to an important role of B-type lamins in organ development, particularly the brain, and should stimulate further research into the function of lamins during tissue development. A growing number of reports further suggest an involvement of lamin B1 in regulating cellular senescence [13]. B-type lamins have recently been linked to two diseases, adult-onset leukodystrophy, caused by a duplication of the *LMNB1* gene [14], and acquired partial lipodystrophy (Barraquer-Simons syndrome) arising from mutations in the *LMNB2* gene [15]. Nonetheless, the number of identified disease-causing mutations remains far fewer than for lamins A/C, suggesting that many lamin B mutations may result in embryonic lethality in humans.

Structural organization of nuclear lamins

Lamins, which are type V intermediate filaments, assemble into a dense network in the nuclear lamina (Fig. 1). Lamins A and C, however, are also present in the nuclear interior [16]. Due to the difficulty of imaging the chromatin- and nuclear membrane-associated lamina at high resolution *in situ* and the challenge to accurately reconstitute the nuclear envelope environment *in vitro*, the ultrastructural organization of the nuclear lamina in mammalian cells remains incompletely understood. Advances in cryo-electron tomography

may eventually enable more accurate visualization of the nuclear lamina in somatic cells [17]. Ectopic expression of human lamins in *Xenopus* oocytes indicates that A-type lamins form a thick (up to 100 nm) network and that B-type lamins form a thin fibrous meshwork closely associated with the inner nuclear membrane, likely due to their farnesyl lipid anchor [18,19]. (See Box 1 for a comparison of common animal models used to study lamins.) Although A-type and B-type lamins can form mixed polymers during *in vitro* assembly [20], immunofluorescence and photobleaching studies suggest that A-type and B-type lamins form separate but overlapping networks in somatic cells [21]. Even lamins A and C segregate and assemble as homodimers *in vivo*, despite their ability to form heterodimers *in vitro* [22]. Whether the diverse lamin networks are interpenetrating or simply adjacent remains to be determined, as well as to what extent specific lamins can compensate for one another. Mice that express only prelamin A, only lamin C, or only mature lamin A lack obvious disease phenotypes [23,24], and in *Drosophila* ectopic expression of an A-type lamin can compensate for loss of B-type lamins in cyst stem cells [25], indicating that lamins may have (partially) redundant or overlapping roles. However, unlike lamin A, ectopic expression of lamin C only partially rescues the native stiffness of lamin A/C-deficient cells [26], suggesting a more important role for lamin A in nuclear stability.

Box 1

Common animal models for the study of lamins

Xenopus oocytes

In the large amphibian oocytes, which express only a B-type lamin (lamin LIII), the lamina lacks the tight association with chromatin seen in somatic cells, allowing easy access to the nuclear lamina and isolation for structural observation by electron microscopy. Its native lamina is organized into orthogonal filaments 10.5 nm wide and spaced 52 nm apart [107]. Lamins from other species ectopically expressed in amphibian oocytes assemble into a nuclear lamina enabling ultrastructural analysis. *Xenopus* oocytes currently present the only model in which the *in vivo* lamina structure can be studied.

C. elegans

These worms express a single lamin, Ce-lamin, that is functionally similar to both A- and B-type lamins [108]. Ce-lamin can be assembled into 10 nm filaments *in vitro*, resembling the organization of the *Xenopus* lamina, although it has been suggested that the 10 nm filaments obtained *in vitro* may represent a transitory phase that remains stable only under certain conditions [108]. The effects of specific lamin mutations in various tissues and their functional consequences can be assessed *in vivo* [58].

Drosophila

Flies express two lamin proteins, A-type Lamin C and B-type Lamin Dm0 [109]. Human lamins expressed in *Drosophila* localize correctly, and many protein interactions are conserved. Many human laminopathies can be modeled by introducing corresponding mutations into *Drosophila* Lamin C. Effects on nuclear structure and organization, as well as functional consequences such as locomotion and lethality, can be assessed in larval and adult animals [109].

Mus musculus

Mice provide important mammalian models to study laminopathies, including *Lmna* mutations causing DCM (N195K, H222P), EDMD (M371K), HGPS (G608G, L530P) and Charcot-Marie-Tooth disease (R298C), as well as various models lacking specific lamin isoforms. The frequently used lamin A/C-null model (*Lmna*^{-/-}), which develops skeletal and cardiac defects, was recently found to express a short (54 kDa) fragment of

A-type lamin by skipping exons 8–11 [110]. In a newer *Lmna*-null mouse model [111], homozygote mice develop more severe phenotypes, whereas heterozygotes remain healthy, implying residual function and mild toxicity of the *Lmna*Δ8-11 fragment. However, ectopic expression of wildtype lamin A in the original *Lmna*^{+/-} cells completely rescues nuclear stiffness in these cells [43], indicating that the *Lmna*Δ8-11 fragment has no dominant-negative effect on nuclear mechanics. While mouse models enable the study of the effect of human lamin mutations in mammals, many models require homozygous expression of the mutant lamin, unlike the often heterozygous expression in human laminopathy patients.

Lamin binding partners

For A-type lamins, at least 54 binding-partners have been identified to date; for the lesser studied lamins B1 and B2, a combined 25 partners have been reported, some of which are also common to A-type lamins [27]. As a note of caution, some of the reported interactions may be indirect or might not occur under physiological conditions, and expression of many binding partners is likely cell-type specific [27,28]. Many nuclear envelope proteins and potential lamin-binding partners are still incompletely characterized, and new partners continue to be discovered. Recent examples include Samp1 [29], MLIP [30] and SLAP75 [31]. Broadly speaking, lamin binding partners can be categorized into structural proteins (such as actin, nesprin, SUN proteins and titin) and signaling molecules and transcription factors (e.g., pRb, ERK1/2, c-Fos, and SREBP), although several proteins may possess both structural and regulatory functions. Importantly, interaction between lamins and lamin-binding partners can take place at the nuclear envelope and/or the nuclear interior, which may provide an additional mechanism to regulate interactions. For a comprehensive overview of lamin-binding partners and their diverse functions, see a recent review [27].

Broken nuclei lead to broken hearts (and muscle) – the effect of lamin mutations

To date, it remains unclear how mutations in lamins, which are nearly ubiquitously expressed, can lead to often highly tissue-specific disorders [2]. The ‘structural hypothesis’ suggests that lamin mutations increase nuclear fragility, resulting in cell death and progressive failure in tissues such as muscle that are exposed to repetitive mechanical stress. The ‘gene regulation hypothesis’ proposes that lamin mutations interfere with tissue-specific genes: lamin mutations may inhibit binding to tissue-specific factors [27] or lead to abnormal gene activation/silencing during differentiation [32]. A third hypothesis proposes that lamin mutations impair stem cell function: mutations may cause abnormal differentiation or depletion of the stem cell niche through defects in proliferation, survival, or differentiation efficiency [25]. These hypotheses are not mutually exclusive, and it is likely that laminopathies arise from a combination of defects in lamin function [2]. For example, abnormal differentiation could be related to dysregulated signaling pathways and disturbed chromatin organization, but also mechanical defects such as impaired nucleocytoplasmic coupling [33]. Recent results provide support for each of these hypotheses, as detailed below.

Lamin mutations can reduce nuclear stability

Nuclear deformability is largely determined by nuclear lamina composition [34–36] and chromatin organization [37,38], which is sensitive to changes in lamin expression [39]. Consequently, expression levels of lamins A (and C) can help predict nuclear deformability, with increasing levels corresponding to stiffer and more viscous nuclei [26,40]. Lamin A/C-deficient nuclei are not only more deformable but also more fragile: lamin A/C-deficient

cells show spontaneous transient nuclear rupture [41] and are more susceptible to nuclear breakage and cell death when exposed to mechanical stress [36]. B-type lamins undoubtedly play an important role in nuclear structure and contribute to nuclear shape and stability, particularly in cells lacking A-type lamins. However, in cells expressing both types of lamins, levels of A-type lamins correlate more strongly with nuclear stiffness than B-type lamins [26,40], suggesting that lamins A and C play a more dominant role in determining nuclear stiffness. This functional difference may be due to different structural properties of the diverse lamin networks, as experiments ectopically expressing human lamins in *Xenopus* oocytes found that A-type lamins assembled into substantially thicker networks than B-type lamins [42]. In addition to lamin content, several other factors may influence nuclear deformability by affecting the organization of the lamin network, including the phosphorylation status of lamins and the structural contribution of lamin-binding proteins.

While earlier studies were directed at cells lacking specific lamins, techniques to assess nuclear mechanics and fragility (e.g., micropipette aspiration, microindentation, and substrate strain application) are now finding widespread application to investigate the effects of specific disease-causing lamin mutations. A recent study of a broad panel of lamin A mutants expressed in lamin A/C-deficient cells found that whereas reintroduction of wildtype lamin A completely restored nuclear stiffness to levels of wildtype cells, many mutations linked to EDMD and DCM failed to restore nuclear stiffness; on the other hand, FPLD mutations were functionally indistinguishable from wildtype lamin A [43]. *In vivo*, muscle tissue from EDMD patients [44], and mouse [45,46] and *Drosophila* models of EDMD and DCM [43,47] contain severely elongated nuclei, indicative of reduced nuclear stiffness. Importantly, lamin mutations responsible for striated muscle disease also increase nuclear envelope fragility. Cultured laminopathy patient fibroblasts have higher rates of nuclear rupture *in vitro* [41], and skeletal muscle and cardiac tissue of mice and human patients carrying EDMD and DCM mutations, respectively, show anecdotal evidence of nuclear rupture *in vivo*, including mitochondria inside the nucleus [48] and discontinuities in the nuclear envelope visible by electron microscopy [49]. Taken together, these results point to a disease mechanism by which lamin mutations cause muscle-specific disease by compromising nuclear envelope stability and integrity, resulting in nuclear rupture and consequently cell death in tissues subjected to mechanical stress.

Contrary to the effect of EDMD- and DCM-causing mutations, lamin A mutations responsible for Hutchinson-Gilford progeria syndrome (HGPS) cause increased stiffness in HGPS patient cells [50,51] and when expressed in *Xenopus* oocytes [19]. Interestingly, fibroblasts from HGPS patients nonetheless have an increased susceptibility to mechanically induced cell death [50]. Increased sensitivity to mechanical stress is particularly relevant to vascular smooth muscle cells in HGPS, as patients and mouse models exhibit a progressive loss of vascular smooth muscle cells in large arteries, which are subjected to repetitive vessel strains.

Lamin mutations cause defects in lamin assembly

The mechanical defects described above are likely caused by aberrations in the nuclear lamina assembly. Similar to other intermediate filament (IF) family members, lamins are composed of a mostly α -helical central rod domain flanked by a short N-terminal head and a long tail domain, which contains a globular Ig-fold [52]. In contrast to cytoplasmic IFs, many questions remain regarding the higher order assembly of nuclear lamins. Most *in vitro* studies have focused on lamins from *C. elegans* (Ce-lamin), which form ≈ 10 nm thick filaments *in vitro*, resembling those observed in the lamina of *Xenopus* oocytes (see Box 1). Mammalian lamins can be induced to assemble into various structures *in vitro*, ranging from short head-to-tail polymers and filaments to paracrystals, depending on the experimental

conditions [43,52]. The physiological relevance of these varying lamin forms remains unclear.

Due to the challenge of crystallizing filamentous proteins, crystallographic analysis has been restricted to smaller lamin fragments, including the coil 2B of lamin A/C [53] and lamin B1 [54], along with the lamin A/C globular tail [55]. Combined with *in vitro* assembly experiments using lamin mutations and partial deletions, these studies indicate that the supramolecular assembly of lamins largely depends on interactions within the lamin rod domains and the N-terminal head domain [52]. These studies have recently been expanded to investigate the effect of specific mutations on lamin assembly. Mutations causing DCM, EDMD and HGPS in the first IF consensus motif and in coil 2 of human [43] and *C. elegans* lamin [56–59] disturb lamin assembly, leading to shortened and irregular filament and paracrystal assembly *in vitro* and increased mobility and solubility of mutant lamins *in vivo* (Fig. 1). The EDMD and DCM-causing mutations in the lamin rod domain impair head-to-tail polymer assembly or lateral filament association rather than lamin dimerization [43], although some mutations could also disturb dimer formation [60,61]. Supporting the notion that EDMD and DCM mutations primarily affect higher order assembly of lamins A/C, the crystal structure of coil2B was recently solved for two DCM mutations, and neither altered the secondary structure of the wildtype protein [62]. Intriguingly, studies with a fragment of the lamin A/C coil 2B domain, comprising a small portion of the tail (residues 328–398), suggest that in addition to the typical left-handed heptad, lamins can form right-handed quindecad coiled-coils [63], so that during head-to-tail polymer formation the IF consensus motifs may “unzip” from the heptad and latch onto the adjacent lamin dimer. Head-to-tail polymer assembly might therefore require that the IF consensus motifs can be easily disassembled, and mutations that increase heptad stability may impede higher order assembly [60].

While the rod and head domains are essential for lamin assembly, other regions are also important for proper protein function. The lamin A/C tail domain, including the globular Ig-fold, harbors most of the interaction sites for lamin-binding partners [27]. Specific mutations can affect the Ig-fold structure in distinct ways. Mutations causing striated muscle disease are typically located in the interior of the Ig-fold beta sandwich, which can destabilize the Ig-fold [55]. In contrast, mutations responsible for FPLD are clustered in a small region on the surface of the Ig-fold. The FPLD mutations, as shown for the R482W mutant, do not affect the crystal structure of the Ig-fold [64], but may instead impair interaction with specific binding partners such as SREBP1 [55]. Lastly, the HGPS mutation that results in a 50 amino acid deletion in the lamin A tail leads to stronger intramolecular binding, impeding molecular interactions that would require accessibility of the Ig fold [65].

Lamin mutations can disrupt nucleo-cytoskeletal coupling

While many lamin mutations that cause DCM and EDMD impair nuclear stability, other mutations have little or no effect on nuclear stiffness [43], suggesting that alternative mechanisms must contribute to the disease. One potential mechanism that has gained increasing prominence is the role of lamins in nucleo-cytoskeletal coupling through interactions with Linker of Nucleoskeleton to Cytoskeleton (LINC) complex components. The LINC complex is composed of SUN protein trimers at the inner nuclear membrane that connect across the luminal space to nesprins proteins on the outer nuclear membrane, which can in turn interact with various cytoskeletal components [66,67]. Intact LINC complex function was recently identified to be crucial for a multitude of cellular functions, including force transmission between the nucleus and the cytoskeleton [68], nuclear positioning in secretory epithelial cells [69], retrograde nuclear movement in migrating fibroblasts via transmembrane actin-associated nuclear (TAN) lines [70], positioning of synaptic nuclei in

muscle fibers [71] and the retina [72], and cytoskeletal organization [36]. Many molecular details underlying LINC complex function, including its dynamic regulation, remain incompletely understood, and recent studies have implicated additional nuclear envelope proteins in nucleo-cytoskeletal coupling, including Samp1 [29,73] and emerin [74]. Lamins A/C can bind to SUN1 [75], SUN2 [76], Samp1 [73], emerin and various nesprin isoforms [77], highlighting their importance in nucleo-cytoskeletal coupling, presumably by anchoring LINC complex components to the nuclear lamina and interior.

Loss of lamins A/C and mutations associated with striated muscle disease can interfere with coupling to SUN proteins [77,78], emerin [59,77], Klaroid (a *Drosophila* nesprin analog) [79], Nesprin-1 [78], Nesprin-2 [80], nuclear pore components [79], and DNA [81]. Conversely, other mutations increase binding to SUN [77] and emerin [82]. Consequently, loss of lamins A/C and lamin mutations responsible for EDMD and DCM can disrupt nucleo-cytoskeletal coupling and related functions. Cells carrying EDMD and DCM mutations have defective intracellular force transmission between the cytoskeleton and nucleus [43], and expression of EDMD and DCM mutations, but not FPLD mutation, prevents retrograde nuclear movement by failing to anchor TAN lines to the nucleus [83]. Lamins also contribute to proper cytoskeletal organization, as lamin A/C-deficient cells have reduced cytoskeletal stiffness and disturbed cytoskeletal networks [36], similar to defects observed in cells after LINC complex disruption. Evidence of impaired nucleo-cytoskeletal coupling can also be found in tissues from EDMD and DCM patients and mouse and *Drosophila* models, which display discontinuous neuromuscular junctions, reduced numbers of synaptic nuclei, abnormal clustering of nuclei, and sarcomere disorganization around the nucleus [44,78,84]. These aberrations could provide further explanation for the muscle-specific phenotype of certain laminopathies.

The role of B-type lamins in nucleo-cytoskeletal coupling is slowly emerging. Lamin B1-deficient cells have spontaneously rotating nuclei, indicating loss of nuclear anchoring, and lamin B1 and B2 are essential for neuronal migration during brain development, a process that involves nuclear movement along microtubules [15,85]. However, the underlying molecular defects remain unclear.

Lamins, mechanotransduction, and gene regulation

The cell nucleus has long been proposed to act as a cellular mechanosensor [86]. Thus, altered nucleo-cytoskeletal coupling and nuclear deformability resulting from lamin mutations may also affect the ability of cells to translate mechanical stimuli into biochemical signals, as evidenced by impaired activation of mechanosensitive genes in lamin A/C- and emerin-deficient cells *in vitro* [36,87] and *in vivo* [88]. However, it remains unclear whether the diminished mechanotransduction signaling results from impaired nuclear mechanosensing or altered downstream signaling. On the one hand, disruption of nucleo-cytoskeletal coupling with dominant negative nesprin and SUN protein constructs, which abolish nuclear deformation when cells are subjected to mechanical strain, has no effect on the mechanical activation of the genes impaired in lamin A/C-deficient cells [68], arguing against a role of the nucleus as a mechanosensor. On the other hand, externally applied forces can alter intranuclear protein mobility [89,90] and depletion of lamins A/C prevents force-induced dissociation of protein complexes inside Cajal bodies [89]. A recent report further found that exposing isolated nuclei to shear stress causes partial unfolding of the lamin A/C Ig-fold, exposing a buried cysteine, which could trigger further signaling events [40]. Furthermore, the ratio of A-type lamins to B-type lamins in cells and tissues strongly correlates with the overall stiffness of the surrounding tissue, with most of the effect being attributed to higher levels of A-type lamins in response to increased tissue stiffness [40]; *in vitro*, increasing substrate stiffness results in higher levels of lamins A/C and suppresses

their phosphorylation [40], which could further increase nuclear stiffness. These findings support the notion that applied forces can directly induce structural changes and signaling inside the nucleus, with the nucleus and the nuclear lamina in particular playing a central role in cellular mechanosensing and adaptation of cells to their mechanical environment. Interestingly, loss of lamin A/C or mutations leading to emerin mislocalization result in impaired intracellular localization of the mechanosensitive transcriptional co-factor myocardin-related transcription factor A (MRTF-A), which plays important roles in cardiac development and function [91]. This effect was caused by dysregulation of the actin-polymerizing function of emerin at the nuclear envelope, affecting nuclear (and cytoskeletal) actin dynamics that are critical in regulating MRTF-A intracellular localization and impairing activation of MRTF-A/SRF downstream genes [91].

Lamins may also modulate gene expression independently of mechanical stimulation, as lamins A/C associate with a number of transcriptional regulators, including c-Fos, ERK1/2, SREBP1, and pRb [27]. Mutations and (functional) loss of lamins can affect intranuclear localization and stability of these transcription factors, as well as the affinity of lamins for specific binding partners. In addition, lamins can modulate gene expression by controlling gene positioning through lamina-associated domains (LADs), which may controls silencing and activation of tissue-specific genes [92]. A detailed discussion of the various gene regulatory roles of lamins can be found elsewhere [2,27].

Given these facts, it is not surprising that lamin mutations can disturb numerous important signaling pathways: striated muscle disease mutations result in abnormal activation of mitogen-activated protein kinases (MAPK) ERK [45], JNK [93] and p38 α [94], as well as target of rapamycin (mTOR) [95,96]; HGPS mutations cause abnormalities in the Wnt pathway [97] and SIRT1 activity [98]. The identification of abnormal signaling pathways provides attractive targets for the development of therapies for laminopathies: treatment with MAPK inhibitors [45,93,94] or rapamycin [95,96] have already been shown to improve phenotypes in EDMD and DCM mouse models. For patients with HGPS, clinical trials with farnesyltransferase inhibitors (FTIs), statins, and bisphosphonates, aimed at modulating the abnormal processing of mutant lamin A, are currently underway [99]. An initial study with farnesyltransferase inhibitors resulted in modestly improved cardiovascular symptoms, but did not rescue the stunted growth of the patients [100]. While the various therapeutic approaches may not always address the root cause of the disease, they nonetheless present powerful means to alleviate many of the most pressing symptoms, immediately benefiting laminopathy patients.

Lamins, cell migration and cancer

An increasing number of reports have recently implicated lamins in human cancers, as cancers of the ovary, colon, gut, blood, prostate, lung and breast often have altered expression of lamins (reviewed in [101]). In the case of colorectal cancer, both increased [102] and decreased levels of lamin A/C [103] have been shown to correlate with increased aggressiveness, with decreased levels associated with tumor recurrence in advanced stage patients [103]. Given the diverse functions of lamins, changes in lamin expression may affect cancer progression through a variety of mechanisms, including altered proliferation, signaling, and migration [101,104]. One possible model to explain how low levels of lamins A/C can contribute to cancer progression is based on the emerging importance of nuclear deformability during cell motility in three dimensional (3-D) environments. It is now becoming clear that nuclear deformability can constitute a rate-limiting factor in the passage of cells through narrow constrictions, as convincingly demonstrated for cancer cells and immune cells migrating through dense collagen matrices [3], breast cancer cells migrating through microfabricated channels [105], and neutrophils passing through microfluidic

constrictions [4]. In the latter case, cells with decreased levels of lamin A were able to pass more easily through constrictions smaller than the size of the nucleus [4]. Conversely, expression of an HGPS lamin variant, progerin, which stiffens the nucleus, impairs cell migration through confining 3-D environments [106], further supporting the idea that nuclear deformability is an important factor in 3-D migration. These findings suggest that downregulation of A-type lamins, whether during physiological processes such as granulopoiesis or in a subpopulation of cancer cells, results in increased nuclear deformability and can thereby facilitate transit of cells through narrow constrictions, for example, in the interstitial space or during intra- and extravasation and passage through narrow capillaries. However, given that lamin levels are not uniformly altered across different cancer types and lamin expression even varies within individual tumors, it remains unclear whether lamins primarily modulate cancer metastasis by changing the mechanical properties of cells or through effects of lamins on cell proliferation, signaling and differentiation.

Concluding remarks

Inside the body, cells are continuously exposed to physical forces and the mechanical constraints of their microenvironment. It is now emerging that lamins play a crucial role in the ability of cells to adapt to their mechanical environment by providing structural support to the nucleus and modulating mechanotransduction signaling. However, it remains unclear to what extent lamins and other nuclear proteins can act as direct nuclear mechanosensors or whether they primarily serve as signaling and structural hubs at the nuclear/cytoskeletal interface. Similarly, the role of lamins in stem cell function and differentiation, e.g., by responding to mechanical cues or tethering genes to transcriptionally repressive locations, remains to be addressed in more detail, as embryonic stem cells lacking all lamins still undergo normal differentiation *in vitro* and *in vivo*. In addition, more work will be required to address the specific effects of lamin mutations associated with different diseases. Patient-derived induced pluripotent stem cells (iPSCs) that can be differentiated into various cell types provide an important tool to study tissue-specific defects of lamin mutations and are finding increasing use in investigating laminopathies. Understanding whether muscle-specific laminopathies primarily result from structural defects or disturbed signaling is particularly relevant to the development of therapeutic approaches; correcting altered signaling is currently more amenable to treatment with small molecules than structural defects, which may require gene therapy or silencing of the mutant gene(s). While much of our current understanding of the diverse functions of lamins has come from studying the effects of disease-causing lamin mutation, it is now becoming apparent that lamins may also play an important role in cancer progression, whether by providing physical limits to the ability of the nucleus to deform through microscopic constrictions in interstitial spaces or by modulating cytoskeletal dynamics and other cell functions.

Lamins provide an ideal research avenue to study the interplay between (nuclear) structure and cellular function, given their central role in modulating nuclear and cytoskeletal structure, gene expression, and a plethora of other cellular functions. Enormous progress has been made in recent years in the understanding of lamins, with insights gained from these studies providing hope and promise to the many patients affected by devastating laminopathies.

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Highlights

Lamins modulate nuclear mechanics, chromatin organization and gene regulation

Lamin mutations cause a broad spectrum of diseases with often tissue-specific defects

Lamin mutations can disrupt nuclear stability and nucleo-cytoskeletal connections

Lamins play an important role in mechanosensing and mechanotransduction signaling

Many cancers have altered lamin expression, which may facilitate metastatic spreading

Figure 1.

Lamin assembly and defects caused by lamin mutations. (A) Experiments with mutated and truncated lamins suggest that different parts of the lamin proteins play distinct roles in lamin assembly (red text). Two parallel lamin monomers (top left) form dimers (top right) through coiled-coil interaction of the heptad repeats in their central rod domains. These dimers assemble head-to-tail by overlapping their rod domains at the two IF consensus motifs (IFCM). The head-to-tail assemblies form non-polar protofilaments composed of two anti-parallel polymers, which then laterally assemble to form mature filaments (and paracrystals) with specific repeat units, visible by electron microscopy and identified as the site of the globular Ig-fold motif. Defects in lamin assembly can be identified *in vitro* as changes in the spacing of the repeat unit, as demonstrated for two mutants in *C. elegans* (bottom), or by failure to form lamin filaments or paracrystals. Note that in the case of the Q159K mutation, it is likely that the spacing is 17/17/17, approximately corresponding to the 48 nm repeat unit, indicating a combination of three overlapping polymers instead of two. Inset, top right: a cross-section view of the heptad repeats of the coiled coil illustrates how the inner amino acids play a role in the dimer assembly, whereas amino acids that point outwards can affect

higher order assembly. (B) Immunofluorescence images of human skin fibroblasts stained for lamins A/C (red), B-type lamins (green), and DNA (blue).

Figure 2. Overview of the diverse functions of lamins in nuclear and cellular mechanics and mechanotransduction.

Table 1

Consequences of lamin mutations on nuclear structure and mechanics

Evidence of altered nuclear stability	Experimental system	References
Nuclear rupture	<i>In vitro</i> : in patient fibroblasts carrying mutations that lead to HGPS, FPLD, RD and HCM <i>In vivo</i> : in the heart tissue of human and mouse carrying DCM mutations	[41] [48,49]
Stiffer nuclei	<i>In vitro</i> : in HGPS patient cells and in <i>Xenopus</i> oocytes overexpressing lamin A with a mutation that causes HGPS	[19,50]
Softer nuclei	<i>In vitro</i> : in fibroblasts carrying mutations that lead to DCM and EDMD <i>In situ</i> : In <i>Drosophila</i> larval muscle expressing dominant-negative lamin mutations	[43]
Elongated nuclei <i>in vivo</i>	In the heart tissue of human, mice, and flies carrying DCM mutations	[43–47]
Defects in lamin assembly	<i>In vitro</i> assembly of lamin filaments and paracrystals from recombinant lamin	[43,56–59]