REVIEW

Recent advances in understanding the role of lamins in health and disease [version 1; peer review: 2 approved]

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Abstract

Lamins are major components of the nuclear lamina, a network of proteins that supports the nuclear envelope in metazoan cells. Over the past decade, biochemical studies have provided support for the view that lamins are not passive bystanders providing mechanical stability to the nucleus but play an active role in the organization of the genome and the function of fundamental nuclear processes. It has also become apparent that lamins are critical for human health, as a large number of mutations identified in the gene that encodes for A-type lamins are associated with tissue-specific and systemic genetic diseases, including the accelerated aging disorder known as Hutchinson-Gilford progeria syndrome. Recent years have witnessed great advances in our understanding of the role of lamins in the nucleus and the functional consequences of disease-associated A-type lamin mutations. Many of these findings have been presented in comprehensive reviews. In this mini-review, we discuss recent breakthroughs in the role of lamins in health and disease and what lies ahead in lamin research.

Keywords

lamins , nuclear envelope , Hutchinson-Gilford progeria syndrome , Lamin Association Domains

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Lamins and the nuclear lamina

Lamins are members of the family of intermediate filaments that are largely but not exclusively localized to the nuclear lamina, a multiprotein mesh structure found on the inner side of the nuclear membrane of most metazoan cells[1–4]. Mammalian cells have two types of lamins: A-type lamins, which are expressed in most terminally differentiated cells, and B-type lamins, which are expressed in most or all somatic cells (Figure 1). A-type lamin A and C are encoded by the *LMNA* gene and generated by alternative splicing, whereas B-type lamin B1 and B2 are encoded by two separate genes: *LMNB1* and *LMNB2*. Short lamin C2 and lamin B3 isoforms encoded by the *LMNA* and *LMNB2*, respectively, are expressed only in gametes[5,6]. Two minor isoforms of lamin A (Δ10) and lamin C (C2) have also been identified, but their function and regulation are not yet fully understood[3]. Lamin A, B1, and B2, but not lamin C, have a carboxy-terminal CaaX motif (C is cysteine, a is an aliphatic amino acid, and X is any amino acid) that undergoes sequential cysteine farnesylation, aaX cleavage, and carboxy methylation. Whereas these modifications are permanent on lamin B1 and B2, lamin A is synthesized as a prelamin A precursor that undergoes an additional processing step catalyzed by the Zn metallopeptidase STE24 (ZMPSTE24) that removes the carboxy-terminal 15-amino-acid tail, including the modified cysteine to generate mature lamin A. Farnesylation is thought to strengthen the association of B-type lamins with the inner nuclear membrane, while the lack of this modification in lamin A and C allows these lamins to be more loosely associated with the nuclear envelope and also occupy the nucleoplasmic space. Lamins are believed to provide a framework that supports the assembly and stability of the nuclear envelope and contributes to nuclear shape and mechanotransduction[1,2,7,8]. Moreover, a growing body of research has provided compelling evidence that lamins make significant contributions to the dynamic organization and function of the genome[1–4,9]. Determining the function of lamins is of critical importance for human health because of the large number of mutations identified across the LMNA gene that are associated with a class of human disorders, collectively known as laminopathies, whose clinical symptoms include skeletal or cardiac muscular dystrophy, lipodystrophy, dysplasia, dermopathy, neuropathy, leukodystrophy, and accelerated aging[9,10]. The discovery in 2003 that Hutchinson-Gilford progeria syndrome (HGPS), a rare premature aging disease that affects children, is caused by a *de novo LMNA* mutation that leads to impaired processing of prelamin A and the production of a permanently farnesylated mutant lamin A protein termed progerin[11,12] has led to an escalation in lamin research with the hope of finding a cure for this devastating disease. Expression of progerin causes severe cellular defects that affect nuclear morphology, chromatin organization, telomere length homeostasis, DNA repair, nucleoplasmic transport, and redox homeostasis[13–17]. Recent studies have provided critical information on the contribution of lamins to nuclear mechanics and the spatial organization of the nucleus (Figure 2) and provided considerable experimental evidence for the hypothesis that lamin A mutations disrupt processes that are critical for nucleocytoplasmic mechanotransduction, nuclear positioning, chromatin organization and function, and responses to stress.

Lamins in nuclear mechanobiology

The nucleus plays a critical role in the response to mechanical forces, and new research adds to a growing body of evidence implicating lamin A/C and the linker of nucleo-skeleton to cytoskeleton (LINC) complexes, which bridge the nuclear lamina to the cytoskeleton, in tissue adaptation to mechanical forces[7,8,18]. Lamins form high-molecular-weight structures, and high-resolution microscopy data have revealed that A- and B-type lamins are organized in a distinct but interdependent meshwork of fibrils[19]. Each of these structures is likely to contribute to maintaining the organization of the nuclear lamina and the shape of the nucleus. Yet the observation that depletion of lamin A/C increases nuclear deformability in response to mechanical stress suggests that lamin

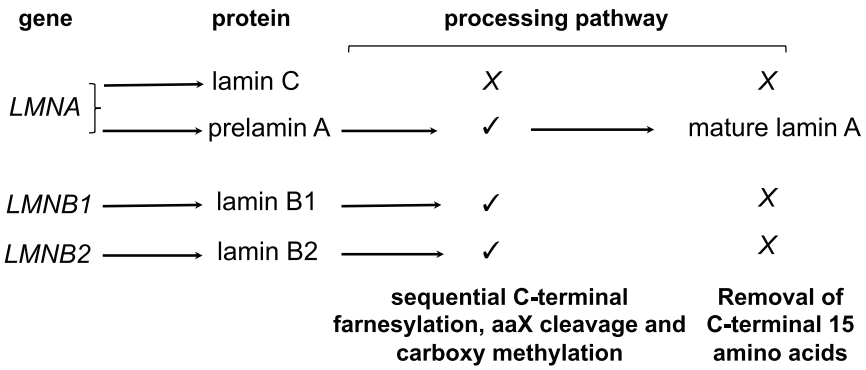

Figure 1. Major A-type and B-type lamins in mammals. Prelamin A, lamin B1, and lamin B2 contain a carboxy-terminal CaaX motif (CSIM in human prelamin A, CAIM in lamin B1, and CYVM in lamin B2; C is cysteine, S is serine, I is isoleucine, M is methionine, A is alanine, Y is tyrosine, and V is valine) which is modified by farnesylation. This is followed by proteolysis of the aaX residues and carboxy methylation at the C-terminal end of lamin A, B1, and B2. Prelamin A undergoes further processing to remove the carboxy-terminal 15 amino acids, including the farnesylated and carboxy methylated cysteine to generate mature lamin A. In Hutchinson-Gilford progeria syndrome cells, the second cleavage site in prelamin A is deleted, and this results in the accumulation of a permanently farnesylated and carboxy methylated prelamin A variant termed progerin. Terminal cleavage of prelamin A is catalyzed by the zinc metallopeptidase ZMPSTE24, an enzyme that has recently been implicated in clearing proteins through clogged endoplasmic reticulum translocon channel[98].

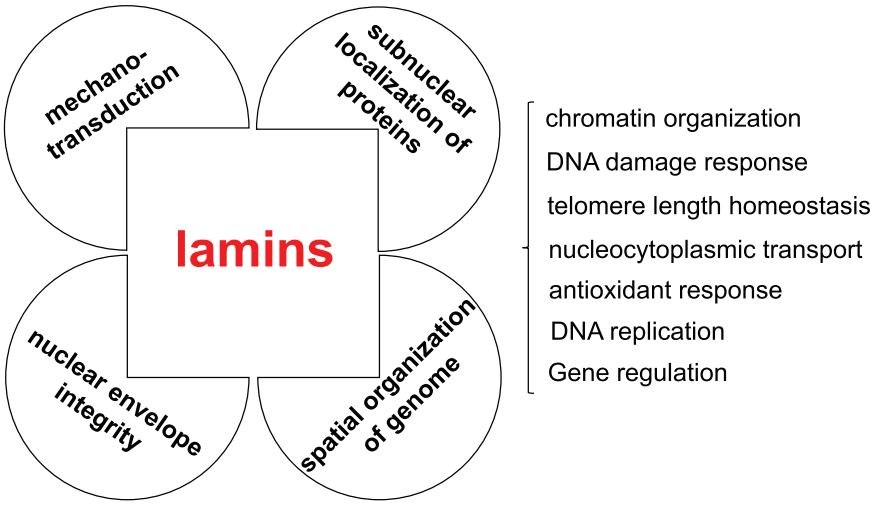

Figure 2. Lamins influence the mechanical properties of the nucleus and contribute to genome organization, function, and stability. Lamins have roles that support various aspects of nuclear structure and function. Lamins provide mechanical strength to the cell nucleus and contribute to cellular mechanotransduction. Lamins influence the nucleoplasmic environment and contribute to shaping the spatial organization of the genome. Lamins influence genome function and stability by contributing, through interactions with various nuclear factors, to the epigenetic regulation of chromatin, DNA replication and repair, and gene transcription.

A/C fibrils play a prominent role in regulating the stiffness and elasticity of the nucleus[20,21]. Consistent with these data, differences in lamin A/C expression leading to changes in lamin A/C-to-B ratio have been demonstrated across distinct cell types, with higher lamin A/C levels observed in cells of tissues often subjected to mechanical torsion, including muscle and heart[22]. Variations in the lamin A/C-to-lamin B ratio have also been observed during hematopoiesis[23], and it is likely that changes in lamin A/C expression affect nuclear stiffness in cancer cells, which may contribute to pathological outcomes, including metastasis[24]. A recent study has also identified force-dependent changes in lamin A/C conformation[25], suggesting that other mechanisms of lamin A regulation contribute to adjusting nuclear shape in response to stress. Research on lamin A/C mutations linked to Emery-Dreifuss muscular dystrophy (EDMD) and dilated cardiomyopathy (DCM) further underscores a role of lamin A/C in nuclear mechanics[26–28]. These studies demonstrated that several disease-causing mutations compromise the stiffness of the nucleus and the integrity of the nuclear envelope, including the nuclear pore complex, in cells of the affected tissues. Remarkably, a recent report showed that muscle structure and function in an animal model of EDMD with tissue-specific alterations in nuclear mechanics are returned to normal by gene inactivation of the enzyme responsible for protein prenylation[29]. Although the precise mechanism underlying this observation remains to be determined, it is possible that changes in the properties, physical interactions, or high-order structure formed by unfarnesylated lamin B confers protection against tissue-specific mechanical stress in this animal model. It is important to point out that not all *LMNA* gene mutations linked to EDMD or DMC, nor mutations associated with familial partial lipodystrophy, result in nuclear fragility[27,29], suggesting that distinct mechanical properties or nuclear functions are affected by different lamin A mutations.

Lamins in chromatin structure and spatial organization of the genome

Within the past few years, efforts have been directed at better understanding the relationship between lamins and genome organization and stability. Both A- and B-type lamins bind DNA *in vitro*[30] and associate with chromatin *in vivo*[2,31], and their loss affects genome integrity[32–34]. Analysis of chromatin-lamin interactions using an *in vivo* tagging approach (DNA adenine methyltransferase identification, or DamID)[35,36] demonstrated that lamins make dynamic contacts with large regions of chromatin, which have been termed lamina-associated domains (LADs), adjacent to the nuclear lamina. These domains are enriched in repressive histone markers, including dimethylated H3K9 and trimethylated H3K27, suggesting that LADs represent a repressive chromatin environment. In spite of these findings, the role of lamins in the formation of LAD remains unclear. A recent study has indicated that lamin C is sufficient for LAD formation at the nuclear lamina[37], and another has questioned the need of any lamin for the formation of these domains[38]. Interestingly, whereas the DamID studies suggested a very high degree of concordance between lamin A/C- and lamin B-associated chromosome domains, recent work using a chromatin-immunoprecipitation approach has identified a subpopulation of lamin A/C that interacts with active regions of chromatin, in coordination with the lamin-associated factor LAP2α[39]. These are likely interactions that occur within the nucleoplasmic space away from the nuclear lamina since LAP2α colocalizes with lamin A/C within the nuclear interior[40,41]. Importantly, both LAP2α levels and the nucleoplasmic pool of lamin A/C are dramatically reduced in the presence of the lamin A mutant progerin[42,43], and these changes are thought to influence processes that are critical for cell proliferation. The conclusion of this and other recent studies on this topic is that a tight balance between lamin A/C and LAP2α must be

maintained to ensure proper cell function, although how this is achieved remains to be worked out. Other studies have also demonstrated that lamins, together with other components of the nuclear lamina termed nuclear envelope transmembrane proteins (NETs), contribute to tissue-specific organization of the genome and influence gene expression by securing peripheral heterochromatin to the nuclear lamina and repositioning genes within the nucleus during cell differentiation[44,45]. The NET lamin B receptor (LBR) has also been recently implicated in the recruitment of the X chromosome to the nuclear lamina to promote X-inactive-specific transcript (Xist)-mediated gene silencing[46]. Taken together with the observation that muscle-specific chromatin reorganization is disrupted in an animal model of EDMD[28], these findings suggest that altered spatial organization of heterochromatin or incorrect positioning of genes contributes to the development of tissue-specific pathologies in at least a subset of the diseases that have been linked to mutations in lamins or NETs.

Lamin A and the mutant progerin have been shown to differentially influence the stability and spatial localization of epigenetic regulators of chromatin structure[31,47], and several studies have reported a gradual decrease in peripheral heterochromatin and global loss of several histone markers of heterochromatin in progerin-expressing cells[48–52]. However, a recent study has added a twist to this story by showing that increased levels of the heterochromatic histone modification trimethyl H3K9 contribute to the development of the progeroid phenotype[53]. The authors demonstrated a direct interaction between lamin A and SUV39h1, a chromatin modifier that is responsible for H3K9me3. Progerin also binds SUV39h1, albeit more tightly than lamin A, which results in increased levels of H3K9me3 in progeria cells. This is an unanticipated result that differs from other studies. A clarification of the type of epigenetic changes caused by progerin requires further investigation, but it is possible, as suggested by the authors of this study, that the decreased heterochromatinization reported by others reflects an *in vitro* cell passage-dependent effect rather than an *in vivo* process. The concept that progerin disrupts lamin A-protein interactions that locally influence chromatin organization is supported by another recent study[54]. In this work, lamin A is shown to recruit chromatin modifiers through interactions with barrier-to-autointegration factor (BAF), a family of proteins that are thought to mediate interactions between various factors and chromatin[55]. As seen with SUV39h1, progerin binds stronger than lamin A to BAF and this interaction results in BAF mislocalization, leading to epigenetic changes that alter chromosome organization and are likely to contribute to cell dysfunction.

Lamins in the regulation of nuclear processes

Fundamental nuclear processes such as transcription, replication, and DNA repair are tightly connected to the spatial organization of the genome and their function relies on the timely recruitment of specific factors to the proper chromosome locations. Recent studies have suggested that progerin disrupts these processes by preventing the recruitment of specific factors to their target site. One example is sirtuin 6 (SIRT6), a protein involved in multiple processes related to genomic stability, stress resistance, telomere maintenance, and energy homeostasis[56]. A study has shown that both lamin A and progerin bind SIRT6, but a stronger interaction with progerin results in SIRT6 sequestration to the nuclear lamina, which prevents SIRT6 from relocalizing to sites of DNA damage. Taken together with prior data showing that progerin affects the function of other DNA repair factors[16], these results underscore the significant hurdle imposed by this mutant lamin A on the pathways that maintain genome integrity. Intriguingly, SIRT6 also plays a role in the recruitment to telomeres of the Werner syndrome protein (WRN)[57], a protein whose loss-of-function mutations cause genetic instability leading to an adult-onset type of progeria[58]. Although it is not known whether WRN function is affected in cells expressing progerin, it is possible that mislocalization of SIRT6 prevents WRN recruitment to telomeres, and this may contribute to telomere dysfunction in HGPS cells. Unfortunately, overexpression of SIRT6 is not sufficient to rescue progeria cell dysfunction, thus limiting the usefulness of potential SIRT6-based therapeutic interventions[59].

In support of the idea that sequestration by progerin is a major mechanism leading to cell dysfunction, it has recently been reported that progerin binds NRF2, a transcription factor that regulates the expression of genes involved in maintaining redox homeostasis[60], and relocates it to the nuclear lamina[61]. Oxidative stress, which has been linked to defective nucleocytoplasmic transport and is likely contributing to persistent DNA damage in HGPS cells[62–66], appears to be a central factor in the pathophysiology of progeria. Since ectopic expression of constitutively active NRF2 ameliorates several of the cellular defects of progeria cells, deregulation of NRF2 function has been suggested to be a primary driver of accelerated aging. Although it is unclear how constitutively active NRF2 escapes sequestration to the nuclear lamina by progerin, these findings suggest that therapeutic approaches that restore NRF2 function may be beneficial to patients with HGPS. Deregulation of NRF2 has also been observed in cells from muscular dystrophy patients expressing certain missense lamin A mutants that tend to mislocalize to the cytoplasm[67]. However, this study reported activation rather than repression of NRF2 in these cells through a mechanism that does not involve lamin A binding.

Therapeutic approaches to Hutchinson-Gilford progeria syndrome

Translation of basic science findings into therapeutic approaches is the uttermost goal of biomedical research. In this regard, the Progeria Research Foundation (http://www.progeriaresearch.org), a non-profit organization founded by the parents of a child with HGPS, has been influential in raising awareness and funds for research on finding a cure for this disease, and these efforts have contributed significantly to the large increase in lamin A research during the last decade. The cellular toxicity of partially processed prelamin A mutants like progerin is due primarily to the presence of the farnesyl group at the carboxy-terminal cysteine. Drugs that inhibit protein farnesyl transferase (farnesyl transferase inhibitors, or FTIs) have been shown to improve the cellular phenotype of progeria cells and ameliorate the pathology of mouse models of the disease[68–79]. FTIs may also hold therapeutic potential for patients carrying EDMD-linked mutations[29]. Driven by these findings, the Progeria Research Foundation sponsored a single-arm clinical trial using the FTI lonafarnib and reported improvements in weight gain, bone structure, and the cardiovascular system of patients with progeria[80]. However, FTIs are far from being a cure for progeria

and better drugs are urgently needed. Since then, a new clinical trial using pharmacological inhibitors of the mevalonate biosynthetic pathway (pravastatin, zoledronic acid, and lonafarnib) has been under way, and preliminary findings have just been published[81]. They indicate that even though the three-drug regimen improves bone size and mineral density, no additional benefit over the one-drug treatment is observed in cardiovascular structure and function. Small molecules that reduce the accumulation of progerin (that is, rapamycin) or influence the microtubule network (that is, remodelin) have recently been shown to have beneficial effects in tissue culture models of progeria[82–84], and they offer new opportunities for therapeutic intervention. Rapamycin may have a therapeutic effect on other laminopathies, since temsirolimus, a rapamycin analog, has been shown to counteract the deterioration of cardiac function in a murine model of cardiomyopathy caused by a lamin A mutation[85]. Future studies in animal models will be crucial to better understand the efficacy and usefulness of these and other new drugs in treating patients with *LMNA* mutations.

Future challenges

The number of articles published on lamins has grown exponentially during the last few years, and tremendous progress has been made in understanding the biological properties of these proteins and lamin A mutants associated with disease. In spite of this gained knowledge, a number of challenges remain. More studies are needed to better understand the relative contributions of lamin A and lamin C to the dynamic spatial organization of the genome in different cell types during development and differentiation. The potential role of lamins in organizing transcription or replication units and DNA damage repair foci needs to be further explored, and future investigations are expected to provide important insights on these topics. Relatively little is known about the molecular mechanisms of tissue-specific disorders caused by *LMNA* missense mutations that do not affect prelamin A processing. A study in cells from a mouse model of DCM has recently shown that expression of a missense mutant N195K-lamin A (N195K) impairs nucleocytoplasmic shuttling of a key factor in cardiac development[86]. These results suggest that a single amino acid change in the lamin A polypeptide induces structural alterations that influence the intracellular distribution and function of a cell-type-specific factor. In a new report, two missense *LMNA* mutations linked to muscular dystrophy (R453W and R482W) have been shown to disrupt LAD and alter heterochromatin organization during myogenic differentiation[87]. These findings strengthen the idea that lamin A/C contributes to the spatial and structural remodeling of chromatin that takes place during cell differentiation. There are hundreds of mutations in the *LMNA* gene known to be associated with tissue-specific diseases[9]. Thus, one may speculate that at least some of these mutations cause tissue-specific defects by affecting the localization or subcellular distribution of factors that, by regulating cell-type-specific regulatory genes or pathways, orchestrate the spatial organization and function of the nucleus. There is also more to learn about the functions of lamin B1 and B2, which, in spite of the high degree of sequence conservation, do not seem to be functionally redundant[88,89]. There is strong evidence that B-type lamins are required for DNA replication, and recent work has identified a specific role for lamin B1 during the elongation phase of this process[32,90–92]. Both lamin B1 and B2 have also been implicated in neuronal migration and survival, and altered distribution of the nuclear pore complex has been observed in lamin B1-deficient cortical neurons[93–97]. This defect has been suggested to affect nucleocytoplasmic shuttling of certain factors[97], which is reminiscent of the cellular defect caused by the lamin A mutation associated with DCM discussed above[86]. These are findings that bring excitement as well as challenges to an area of research that is predicted to expand further over the next several years.

Abbreviations

BAF, barrier-to-autointegration factor; DamID, DNA adenine methyltransferase identification; DCM, dilated cardiomyopathy; EDMD, Emery-Dreifuss muscular dystrophy; FTI, farnesyl transferase inhibitor; HGPS, Hutchinson-Gilford progeria syndrome; LAD, lamina-associated domain; LAP2α, lamin-associated protein 2α; NET, nuclear envelope transmembrane protein; SIRT6, sirtuin 6; WRN, Werner syndrome protein.

Competing interests

The authors declare that they have no competing interests.

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