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Nuclear Lamin Functions and Disease

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Recent studies have shown that premature cellular senescence and normal organ development and function depend on the type V intermediate filament proteins, the lamins, which are major structural proteins of the nucleus. This review presents an up-to-date summary of the literature describing new findings on lamin functions in various cellular processes and emphasizes the relationship between the lamins and devastating diseases ranging from premature aging to cancer. Recent insights into the structure and function of the A- and B- type lamins in normal cells and their dysfunctions in diseased cells are providing novel targets for the development of new diagnostic procedures and disease intervention. We summarize these recent findings, focusing on data from mice and humans, and highlight the expanding knowledge of these proteins in both healthy and diseased cells.

Nuclear lamin structure and assembly

The nuclear lamins are the major structural proteins of the nuclear lamina, which is located in the peripheral region of the nucleus between the inner nuclear envelope membrane and chromatin. In addition, lamins are distributed throughout the nucleoplasm, but at significantly lower concentrations than at the nuclear lamina. Genetic analyses have revealed that lamin genes are highly evolutionarily conserved in metazoans, but are not found in plants or unicellular organisms [1]. The lamins are subdivided into A- and B-types, both of which belong to the type V intermediate filament protein family. Lamin A and lamin C are alternative splice variants of the *LMNA* gene [2], and lamin B1 and lamin B2 are derived from two different genes, *LMNB1* and *LMNB2* [3]. Lamin proteins exhibit extensive sequence similarity in their N-terminal “head”, central α -helical rod and carboxy-terminal “tail” domains. The tail domains of all lamins contain a nuclear localization signal and an Ig-fold motif [1]. Lamins A, B1 and B2 are initially synthesized as precursors termed pre-lamin A, pre-lamin B1 and pre-lamin B2. The processing of these precursors into mature lamins A, B1 and B2 involves a sequential series of post-translational modifications [3], beginning with farnesylation of the cysteine residue in the C-terminal CaaX motif, followed by the subsequent cleavage of the aaX residues by specific endoproteases, such as RCE1, which cleaves lamin B1 [4], and ZMPSTE24, which cleaves lamin A [5], and then the methylation of the farnesylcysteine by isoprenylcysteine carboxyl methyltransferase (ICMT) [6]. Lamin A is further processed by the ZMPSTE24-catalyzed removal of a 15 amino acid

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farnesylated carboxy terminal peptide [7]. It has been suggested that the farnesylation and methylation steps may be involved in targeting lamins to the nuclear periphery and stabilizing their interactions with the inner nuclear membrane, although prelamin A processing appears to be dispensable in mice [8].

Biochemical studies have shown that purified lamins assemble into higher-order filamentous structures *in vitro* [3]. This involves a multi-step process initiated by dimerization of lamin monomers and head-to tail interactions of coiled-coil dimers to form protofilaments [9]. *In vitro*, these protofilaments associate laterally and ultimately lead to the formation of highly ordered paracrystalline arrays [3, 9, 10]. Recent evidence suggests that lamins can form both homodimers and heterodimers, suggesting that lamin filaments could assemble into protofilaments composed of both A- and B-type lamins [11]. Alternatively, it is possible that protofilaments formed from only A-type or B-type lamins could associate laterally to form mixed higher order lamin structures.

In contrast to what is known about the lamin assembly process *in vitro*, little is known about lamin assembly and structure within nuclei, although it has been suggested that the formation of a lamin network in cells is a self-organizing process [12]. Recent studies have demonstrated that the nuclear lamina in cells is composed of separate, but interacting, A-type or B-type fibrillar meshworks [13]. High-resolution confocal microscopy reveals a separation of A- and B-type lamin filaments with some sites of overlap. However, silencing the expression of individual lamin isoforms can lead to changes in and sometimes disruption of the remaining lamin network structures. This frequently leads to the formation of misshapen nuclei, suggesting that the individual lamin networks must physically interact. Furthermore, both the silencing of lamin B1 expression and the expression of some mutant forms of lamin A cause misshapen nuclei. Many of these misshapen nuclei possess nuclear envelope blebs that are enriched in enlarged lamin A/C networks, but are devoid of B-type lamins [13, 14]. Surprisingly, mouse fibroblasts expressing only mature lamin A have misshapen nuclei similar to those seen in laminopathy patient fibroblasts, but the mice have no apparent defects [8].

B-type lamins in proliferation and development

The B-type lamins are expressed in most cell types independently of their differentiation states, while the expression of lamins A/C is thought to be restricted to differentiated cells [15]. These observations have led to the suggestion that B-type lamins may have important roles in the regulation of DNA replication, cellular differentiation, cell proliferation, gene expression, developmental processes, and life span [3]. This is supported by the observation that silencing of lamin B1 or B2 expression in HeLa cells induces apoptosis [16]. Other studies on the role of B-type lamins in cell proliferation have painted a complex picture of the roles of lamins in cell proliferation. Fibroblasts prepared from mice with an insertional mutation in *Lmnbl* have misshapen nuclei, increased polyploidy, and impaired differentiation, and they become prematurely senescent [17]. However, conditional knockouts for *Lmnbl* and *Lmnbl2* in mouse skin keratinocytes develop normally and isolated keratinocytes proliferate normally in culture [18]. Embryonic stem cells (ESC) from different B-type lamin knockout mice have no obvious nuclear or proliferative abnormalities and only minor changes in their transcription profile in comparison to wild-type mouse ESCs [19]. In contrast to these mouse knockout studies, the silencing of lamin B1 expression in normal human diploid fibroblasts (HDFs) causes a proliferation defect and triggers rapid premature senescence [20]. Furthermore, lamin B1 protein and mRNA levels are reduced both in normal cellular senescence and in premature senescence induced by oncogenic Ras [20].

Although the mechanisms by which lamin B1 regulates cell proliferation are unknown, some insights come from the findings that the senescence induced by silencing lamin B1 expression requires activation of the p53 and Rb pathways and is independent of both telomere dysfunction and accumulation of DNA damage. Surprisingly, lamin B1 silencing also causes a transient decrease in mitochondrial reactive oxygen species (ROS) through activation of the p53 pathway and upregulation of various antioxidant genes including SOD1/2. This decrease in ROS level appears to be responsible for the cellular proliferation defects in lamin B1 silenced cells. Furthermore, overexpression of lamin B1 in HDFs increases their proliferation rate and extends their lifespan [20]. Together these experiments suggest that lamin B1 plays an important role in regulating HDF proliferation [20]. Interestingly, another study has recently shown that lamin B1 levels are increased when HDFs are induced to become senescent by oxidative stress or oncogenic Ras [21]. By contrast, silencing of lamin B1 expression in mouse fibroblasts [22] causes an increase in ROS levels, possibly reflecting differences in the susceptibility to oxidative stress between human and mouse fibroblasts [23]. The discrepancies in lamin B1 expression levels detected during senescence among these studies remains to be resolved.

Surprisingly, neither lamin B1 nor B2 are required to complete embryogenesis in mice; however, the mice die immediately after birth. Lamin B1 null mice die from respiratory failure due to poorly developed diaphragms and lungs with smaller alveoli. These mice also have bone abnormalities, microcephaly, and undeveloped cerebral cortices [19, 24, 25]. Interestingly, *Lmnb2* null mice are born with significantly fewer organ abnormalities, but development of the cerebral cortex and cerebellum are severely impaired due to the defective migration of neurons from the ventricular zone to the cortical plate [19, 24, 25]. The importance of the B-type lamins in brain development is further emphasized in mice carrying forebrain specific conditional knockout alleles for *Lmnb1* and *Lmnb2* [25]. These double knockouts exhibit even more severely disorganized cortical structures [25]. Although the specific roles played by the B-type lamins in normal mouse brain development remain unknown, it has been suggested that a normal nuclear lamina composition is required for proper mitotic spindle orientation in neural progenitor cells, nuclear elongation in neurons, neuronal migration, and the organization of different brain compartments [18, 19, 24–26]. Thus, these recent findings suggest that the B-type lamins are essential for the development of specific tissues and organs such as brain and lung, but may not be required in general for cellular proliferation or differentiation.

Lamin B2 may also have cytoplasmic functions. Recently, lamin B2 was identified as a locally translated protein in *Xenopus* retinal ganglion cell axons [27]. Remarkably, lamin B2-depleted axons exhibit mitochondrial dysfunction, defects in axonal transport, and axonal degradation. The importance of B-type lamins in neuronal tissues is underscored by the observation that the expression of prelamin A is very low or nonexistent in the neurons and glia cells of mouse brain [28]. The expression of prelamin A, lamin A, and the major lamin A mutant causing progeria, appear to be specifically down-regulated by miR-9, a brain specific microRNA. These findings may ultimately explain the absence of central nervous system pathologies in HGPS patients.

Lamin B-associated disorders

Disease-causing mutations in the human *LMNB1* and *LMNB2* genes are extremely rare. The most extensively studied of these, adult-onset autosomal dominant leukodystrophy (ADLD), is caused by duplication of *LMNB1* [29]. The pathology of this disease includes slow degeneration of myelin in the central nervous system followed by pyramidal signs, ataxia, and impaired cardiovascular reflexes due to the absence of sympathetic nerve functions [30–32]. In most cases of ADLD, increased expression of lamin B1 has been

detected in peripheral leukocytes [31]. Increased lamin B1 expression has also been detected in a variant of ADLD where neither gene copy-number defects nor point mutations in *LMNB1* are found. It appears that a mutation in an *LMNB1* regulatory sequence is responsible for this phenotype [33]. At the cellular level, overexpression of lamin B1 creates disorganization of inner nuclear membrane proteins and chromatin. Additionally, myelin gene expression is down regulated and myelin proteins become mislocalized in ADLD brains. The microRNA *miR-23* appears to be a negative regulator of lamin B1 expression and may be important in this disease pathology [34]. Lamin B1 over expression is also seen in Ataxia Telangiectasia (A-T) and the normalization of its expression level reduces nuclear shape defects and the premature senescence of patients' cells [21]. Interestingly, overexpression of the *Drosophila* lamin B1 ortholog, Dm0, induces a degenerative phenotype in the cells of the eye, neuronal death, and shortened lifespan [35]. These findings emphasize the importance of determining the mechanisms involved in the regulation of lamin B1 expression and its specific functions in different species and cell types.

Human lamin A mutations

Approximately 300 mutations have been mapped to the human *LMNA* gene (Figure 1). These are associated with different disorders, which collectively with B-type lamin-associated diseases, are referred to as laminopathies (see Table 1; reviewed in [36]). Extensive studies of the cells of Hutchinson-Gilford Progeria Syndrome (HGPS) patients have shown that progerin, the irreversibly farnesylated mutant form of lamin A, localizes mainly to the nuclear periphery, but does not properly incorporate into the lamina [3]. Furthermore, progerin expression causes nuclear lobulation and blebbing, interferes with normal mitotic progression, and induces abnormal chromosome segregation, binucleation, genomic instability, and premature senescence in both HGPS and normal fibroblasts (Figure 2a) [37, 38].

There appears to be no correlation between the expression of progerin and the allelic location of the mutation [39], even though the mRNA level of progerin differs significantly among HGPS patient samples and those obtained from normal aged people [40]. With respect to this latter finding, it is very interesting that progerin expression has been detected in the coronary arteries of normal individuals between the ages of 1 month and 97 years, with an increase in expression of ~3.34% per year [41]. Even though adventitial fibrosis and other cardiovascular pathologies are more prominent in HGPS patients, there is a high correlation between the expression of progerin and cardiovascular pathology among geriatric patients [41]. There is also evidence that progerin accumulates in different tissues of normal individuals as a function of age [40–42], suggesting that progerin expression may play a role in normal aging [38]. Therefore it has been suggested that progerin levels may serve as a useful biomarker of human aging and age-dependent vascular diseases [38, 43, 44]. Notably, other mutations in *LMNA* that are not associated with progerin expression also cause premature aging disorders. These are classified as atypical progeria syndromes (APS). Patients with APS have variable clinical characteristics including short stature, partial alopecia, skin atrophy over the hands and feet, diabetes, generalized lipodystrophy, and mandibular hypoplasia [45]. These diseases also share several cellular phenotypes with HGPS, including blebbed/lobulated nuclei, aneuploidy, and premature senescence (Figure 2b) [46]. Another progeroid disorder which is similar to HGPS is caused by a homozygous mutation in *ZMPSTE24* together with a heterozygous mutation in *LMNA* (1960C>T) [47].

Insights into the molecular mechanisms involved in progeria and premature senescence

Because there have been several recent reviews emphasizing the molecular mechanisms responsible for the different laminopathies [48, 49] we have chosen to review only the more recent insights into the mechanisms responsible for HGPS and other progeroid phenotypes. Cells from different laminopathy patients including progeria share several aberrant nuclear phenotypes, including nuclear shape abnormalities, impaired mitosis, abnormal organization of heterochromatin, delays in the cell cycle, accumulation of DNA damage, and premature replicative senescence [37, 42]. However the molecular mechanisms responsible for these abnormalities have not yet been identified. Given the proposed roles for lamins in regulating transcription, it is possible that mutant lamin A/C proteins causing progeria alter gene expression patterns [3]. Comparative microarray analyses of HGPS and control fibroblasts reveal that 352 genes are differentially expressed when progerin is present. The majority of misregulated genes are involved in lipid metabolism, cell growth and differentiation, DNA replication and damage repair, development of the cardiovascular system, and the cell cycle [50]. Despite these changes, no direct correlations have been made between alterations in gene expression and the mechanisms responsible for HGPS. One possible explanation for the lack of such correlations may be related to the finding that the expression of progerin has significant effects on histone modifications and a dramatic reduction in peripheral heterochromatin in the cells of affected patients [3]. The degree and extent of the changes in histone modifications, chromatin organization, and genome-wide alterations in gene expression are likely related to the level of progerin expression [3]. In turn these changes could affect the capacity of cells to respond to stress caused by, for example, DNA damage.

Support for this comes from the finding that defective DNA damage repair is correlated with the accumulation of permanently farnesylated lamin A in both HGPS [51] and in *Zmpste24*^{-/-} mouse fibroblasts [51–53]. The *Zmpste24* null cells accumulate γ H2AX, have altered histone H3 and H4 methylation patterns, and exhibit decreased expression of HP1 [3]. Additional changes in these cells include activation of the DNA repair regulating factors ATM, ATR, p53, and check point kinases, which is likely to contribute to impaired cell cycle progression and replication arrest [51, 54]. In HGPS cells, the recruitment of DNA repair proteins including 53BP1, Rad50, and Rad51 to sites of induced DNA damage is significantly delayed, leading to the accumulation of unrepaired DNA [53]. In a similar fashion, hypoacetylation of histone H4 in *Zmpste24*^{-/-} fibroblasts has been linked to the misregulation of Mof, a histone acetyltransferase. Treatment of these cells with a histone deacetylase inhibitor causes an increase in DNA damage repair due to the improved recruitment of DNA repair proteins [55]. HGPS fibroblasts also have significantly higher basal levels of ROS, as well as a greater sensitivity to ROS exposure, factors known to increase DNA damage. This defect can be ameliorated with the ROS scavenger n-acetylcysteine, which also significantly reduces the level of double strand breaks (DSB) [56, 57]. Recent studies suggest that impaired interactions between A-type lamins and signaling proteins such as Rb and/or DSB repair proteins such as Ku-70 and DNA-PKcs may be involved in this reduction [58]. Alternatively, there is evidence that the expression of essential DNA damage repair factors such as BRCA1 and Rad51 may also be affected by alterations in lamin A, thereby promoting the accumulation of DNA damage and increasing sensitivity to DNA damaging agents [59]. Based upon all of the available data from patient cells and mouse models, it appears that the elevation of ROS, alterations to histone modifications, and the impaired recruitment of DNA repair proteins to sites of DNA damage are significant causative factors in HGPS. However, the specific functions of lamin A in these pathways, including DNA damage repair and regulation of ROS, remain to be determined.

Other possible causes of the premature senescence observed in human fibroblasts expressing mutant A-type lamins are accelerated telomere shortening, induction of telomere dysfunction, and uncontrolled DNA damage signaling [60–62]. For example, there is both an abnormal distribution of telomeres and telomere shortening in *Lmna*^{−/−} MEFs. It has also been shown that the 53BP1-mediated non-homologous end joining repair of dysfunctional telomeres requires lamins A/C [62]. Interestingly, telomere damage during replicative senescence in normal fibroblasts increases the production of progerin, suggesting a possible synergy between telomere structure and progerin expression in cellular senescence during normal aging [63]. In support of a role for telomeres in HGPS progression, expression of the catalytic subunit of telomerase extends the lifespan of HGPS cells [60, 64]. Hence, it appears that both the permanently farnesylated lamin A produced in the *Zmpste24*^{−/−} mouse cells and progerin can promote premature cellular senescence due to genomic instability related to the accumulation of DNA damage and the deregulation of telomere processing.

Lamins in cancer

Alterations in nuclear morphology have been used by pathologists to identify and evaluate cancer cells since the 19th century. Morphological changes in nuclear shape, size, lobulation (Figure 2c), and the appearance of heterochromatin and nucleoli are all used to determine the stage of tumor development and to make a prognosis (reviewed [65]). For example, one of the best known diagnostic histopathological tests is the Papanicolaou (PAP) smear test for cervical cancer. This test involves an assessment of the nuclear shape of exfoliated cervical cells. In addition, nuclear pleomorphism is widely used in the diagnosis, grading, evaluation, and prognosis of breast [66], renal [67, 68], lung, [69] and other cancers. Despite the long history of the use of tumor-related nuclear structural changes in cancer cells little is known about the relationship between these changes and the nuclear lamins.

It is certainly likely that the changes in nuclear architecture which represent the pathological hallmarks of cancer cells are related to alterations in the lamins. This idea is based upon their emerging roles as major players in regulating many nuclear housekeeping functions [70]. In support of this, heterogeneous expression of nuclear lamins, especially lamins A/C, has been observed in tumor cells obtained from cancers of the ovary [71], colon [72], gut [73], blood [74], prostate [75], lung [76], and breast [71, 77]. In colon cancer, a correlation between low expression levels of A-type lamins and increased recurrence in stage II and III colon cancer patients has been reported [78, 79]. These observations have led to the proposal that the expression of lamin A/C can serve as a risk biomarker [72] and may also be considered as a prognostic indicator in colorectal cancer (reviewed in [80]). Interestingly progerin expression has been associated with cell transformation and tumor growth in prostate and breast cancer cell lines [81]. Because aging is a major risk factor for cancer, the expression of progerin in aging cells and its putative influence on the DNA damage repair pathways may contribute to tumor development. However, it should be noted that there is no evidence of increase cancer incidence in HGPS patients, which may be related to the early death of patients in the second decade of life.

The expression of the B-type lamins has not been extensively explored in cancer, although decreases in lamin B1 expression have been observed in neoplasms of the gastrointestinal tract [82] and in subtypes of lung cancer [83]. By contrast, it has been reported that lamin B1 expression is increased in malignant prostate cancer and that this can be used as a tumor differentiation and prognostic marker [84]. One study of hepatocellular carcinoma has shown that lamin B1 levels increase in tumors and in patient's plasma [85]. Recently, lamin B deficient and lamin A/C-enriched microdomains have been described in the nuclear envelopes of prostate cancer cells. These microdomains are associated with specific chromosomal regions and decreased expression of genes in these regions [75]. It is

important to note that all of these reports of changes in lamins in cancer cells are only of a preliminary nature. Much more thorough investigations are required to determine the specific functions of lamins in the transformations of cells that occur in cancer as well as their utility in tumor diagnosis and prognosis.

Concluding remarks

Recent studies have revealed that the nuclear lamins are major building blocks of nuclear architecture not only with respect to their classical roles in establishing and maintaining the mechanical integrity to the nucleus, but also in the maintenance of genomic stability, regulation of DNA damage repair, gene expression, differentiation, proliferation, and senescence. The evidence available at the present time suggests that A- and B-type lamins have relatively non-redundant functions. Recent studies demonstrate that the expression and function of each of the lamins are highly regulated and their expression levels appear to be correlated with the stage of cell differentiation. The current escalation of new discoveries in the nuclear lamin field suggests that future explorations of the specific roles of the different lamin isoforms and their post-translational modifications will reveal great surprises regarding their functions in both the nucleus and the cytoplasm of vertebrate cells.

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Box 1. iPSC models of the laminopathies

Induced pluripotent stem cell lines (iPSC) have been derived from fibroblasts obtained from patients with typical HGPS [58, 86], inherited dilated cardiomyopathy (DCM), atypical Werner syndrome (aWS), and APS [87] to explore the roles of mutant lamins A/C in cellular pathology. Analyses of HGPS iPSCs prepared from early passage cells showed that they did not express either wild-type lamins A/C or progerin. In addition, the nuclear morphologies and karyotypes of these iPSCs appeared normal and were indistinguishable from those of human ESCs or iPSCs derived from normal fibroblasts [58, 86, 87]. Interestingly, when HGPS-iPSCs and control iPSCs were compared, alterations in epigenetic modifications were detected in only 33 autosomal genes, none of which have a significant function [58]. This suggests that chromatin instability and changes in the transcription profile of HGPS cells depends on the expression of progerin. Upon differentiation of these HGPS-iPSCs into mesenchymal stem cells (MSCs), vascular smooth muscle cells (VSMC) [86], smooth muscle cells (SMCs) [58] or disease related secondary fibroblasts [87], *de novo* expression of both lamins A/C and progerin were detected. As was previously shown with HGPS patient cells [3] progerin levels in HGPS-iPSCs increased with passage number, and this was correlated with increased DNA damage, nuclear blebbing and lobulation, slower proliferation, loss of the heterochromatin mark H3K9me3, and premature senescence [58, 86, 87]. Interestingly, neural progenitor cells derived from HGPS-iPSCs cells expressed only low levels of progerin with increasing passage number and their further differentiation appeared indistinguishable from controls [86]. In contrast, VSMCs and MSCs derived from HGPS-iPSCs displayed higher levels of progerin accumulation with an increase in the number of DNA damage foci and nuclei with abnormal shapes. These cells were also more sensitive to hypoxia and mechanical stress when compared with control iPSCs [86]. These findings suggest that human iPSC models of laminopathies will be useful in determining the molecular mechanisms responsible for the cellular changes that take place in these diseases.

Box 2. Animal models of the laminopathies

Mouse models that mimic many of the phenotypic characteristics of human laminopathies have been used to investigate the effects of lamin A mutations on various tissues and to develop and test possible therapies for HGPS, EDMD2, lipodystrophy, and dilated cardiomyopathy [88].

Many aspects of the pathology of human HGPS patients have been replicated in mouse models such as the *Lmna* null mouse (*Lmna*^{-/-}) with an HGPS knock-in allele (*Lmna*^{HG}), or with *Zmpste24*^{-/-} mice lacking the metalloproteinase needed for the maturation of prelamin A [89]. These mice express only a farnesylated form of lamin A, and oral administration of a farnesyltransferase inhibitor (FTI) beginning at birth is sufficient to significantly ameliorate bone and cardiovascular defects, although life span was only marginally extended [90]. Mice expressing only a non-farnesylated form of progerin (*Lmna*^{csmlHG}) were normal [91]. Together, these studies strongly implicate the accumulation of farnesylated progerin as the causative factor in HGPS pathogenesis and suggest that FTI treatment can ameliorate disease symptoms when the drug is administered early in the disease. The success in ameliorating the progerin-related defects in both mouse and cell models has led to drug therapy trials in HGPS patients with inhibitors of protein farnesylation [92, 93], such as the FTI Lonafarnib or a combination of statins and aminobisphosphonates [94]. The latter two drugs are widely used for the prevention of cardiovascular disease and bone loss, respectively, and are well tolerated [95, 96]. The importance of long term studies at the cellular level is supported by the recent finding that FTI treatment of normal cells causes a centrosome separation defect resulting in the formation of donut-shaped nuclei. These cells do not undergo apoptosis or become senescent, but continued to divide abnormally, ultimately becoming aneuploid. These effects appear to be in part mediated by the degradation of lamin B1 and pericentrin [97]. Other alternative treatments for HGPS have included attempts to improve the balance between growth hormone and insulin-like growth factor 1 (GH/IGF-1), which delays the appearance of progeroid features and extends the lifespan of *Zmpste24*^{-/-} mice. In addition, rapamycin treatment of HGPS patient fibroblasts appears to abolish nuclear blebbing and this is correlated with enhanced degradation of progerin, improved genome stability, and delayed onset of cellular senescence [63]. These findings suggest that other treatments either administered alone or in combination with inhibitors of farnesylation may benefit HGPS patients.

Figure 1.

A partial summary of mutations in lamin A/C. The mutations are categorized into those involving primarily adipose tissue (lipodystrophy) (orange), cardiac muscle (cardiomyopathy) (blue), skeletal muscle (muscular dystrophy and myopathy) (green), and premature aging (atypical Werner's, HGPS, atypical progeria) (red). Due to the large number of mutations identified in *LMNA*, only those mutations resulting in amino acid substitutions resulting in the production of a full length lamin A/C are included, with the exception of the 50 amino acid deletion in HGPS. Other mutations involving deletions, premature stop codons, and insertions are not included. The information on mutations and their associated diseases was obtained from the Leiden Muscular Dystrophy pages (www.dmd.nl/lmna) and the Human Intermediate Filament Database (www.interfil.org) [98].

A. HGPS

B. APS

C. Breast cancer

Figure 2.

Changes in the nuclear envelope/lamina of HGPS, APS, and cancer cells. **(A)** Double labeling with lamin A/C (red) and lamin B (green) of an HGPS cell [37]. **(B)** Flower-shaped nucleus of an APS cell with the E145K mutation stained for lamin A (red) and centromeres (CREST antiserum, green) showing that centromeres are clustered in the central region of the nucleus instead of their normally dispersed nuclear distribution [46]. **(C)** Metastatic breast cancer cell MDA MB435 labeled for lamin A/C (red) and lamin B (green).

Table 1

Syndrome/disease	Effects on <i>LMNA</i> gene and protein	Phenotype
Emery–Dreifuss muscular dystrophy (EDMD)	Autosomal dominant or recessive missense mutations in <i>LMNA</i> in various positions. Some may affect assembly of lamin A and interactions with associated proteins.	Progressive muscle weakness, cardiomyopathy
Dilated cardiomyopathy, type 1A	Autosomal dominant missense mutations mostly in exons 1 or 3 of <i>LMNA</i> .	Cardiomyopathy with minimal effects on skeletal muscle
Limb girdle muscular dystrophy (LGMD)	Autosomal dominant mutations in exon 1 of <i>LMNA</i> . The effect on lamin A is not known.	Skeletal muscle weakness and heart defects
Familial partial lipodystrophy, Dunnigan type (FPLD2)	Autosomal dominant missense mutations in exons 8 and 11 of <i>LMNA</i> . Mainly affects the Ig-fold domain that may interfere with protein-protein interactions.	Loss of subcutaneous fat, insulin-resistance, diabetes, hypertriglyceridemia and atherosclerosis
Mandibuloacral dysplasia (MAD)	Autosomal recessive mutations R527H, K542N, and A529V in the Ig-fold domain. Compound heterozygous mutations have also been reported. May interfere with protein-protein interactions.	Dental defects, lipodystrophy, atrophy of the skin on hands and feet, mandibular hypoplasia, acroosteolysis, alopecia, insulin resistance, progeroid features.
Hutchinson–Gilford progeria syndrome (HGPS)	Mostly spontaneous mutations (1824 C-to-T) in exon 11 of <i>LMNA</i> . This activates a cryptic splice donor site leading to the permanently farnesylated form of mutant lamin A called “progerin” with a deletion of 50 amino acids near the C terminus. Alters lamin functions with respect to nuclear shape maintenance and chromatin organization.	Early onset premature aging with alopecia, loss of subcutaneous fat, severe atherosclerosis, and cardiovascular disease leading to early death.
Atypical progeria syndromes (APS)	Various heterozygous missense mutations in <i>LMNA</i> , which are not associated with the production of progerin. These include heterozygous missense <i>LMNA</i> mutations, such as, P4R, E111K, D136H, E159K, and C588R.	Associated with different progeroid features including one or more of the following: short stature, partial alopecia, diabetes, lipodystrophy and mandibular hypoplasia, and cardiovascular disease.
Atypical Werner’s syndrome (AWS)	Autosomal dominant mutations A133L mutation in <i>LMNA</i> . Effect on protein is unknown, but may lead to changes in protein-protein interactions.	Late onset premature aging, atherosclerosis, sclerodermatous skin, premature grey hair.
Restrictive dermopathy (RD)	Mutations in exon 11 of <i>LMNA</i> and/or homozygous or compound heterozygous mutations in <i>ZMPSTE24</i> . These result in the formation of permanently farnesylated pre-lamin A.	Loss of fat tissue, tight skin, pulmonary hypoplasia, early lethality.
Charcot–Marie–Tooth disease, type 2B1	Autosomal recessive missense mutations in the lamin A rod domain that may affect lamin assembly.	Weakness and areflexia of lower limbs
Generalized lipodystrophy	Autosomal dominant mutations I10T and heterozygous substitution in exon 1 c.29C>T, in <i>LMNA</i> with unknown effects on lamin A.	lipodystrophy or lipoatrophy, may include diabetes and a progeroid phenotype