HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Gastroenterology. 2018 May ; 154(6): 1602–1619.e1. doi:10.1053/j.gastro.2018.03.026.

Lamins and Lamin-associated Proteins in Gastrointestinal Health and Disease

Graham F. Brady[1,2,#], **Raymond Kwan**[1], **Juliana Bragazzi Cunha**[1], **Jared S. Elenbaas**[3], and **M. Bishr Omary**[1,2,4]

[1]Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, Michigan [2]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan [3]Medical Scientist Training Program, Washington University, St Louis, Missouri [4]Åbo Akademi University, Turku, Finland

Abstract

The nuclear lamina is a multi-protein lattice composed of A-and B-type lamins and their associated proteins. This protein lattice associates with heterochromatin and integral inner nuclear membrane proteins, providing a link between the genome, nucleoskeleton, and cytoskeleton. In the 1990s, mutations in *EMD* and *LMNA* were linked to Emery-Dreifuss muscular dystrophy. Since then, the number of diseases attributed to nuclear lamina defects, including laminopathies and other disorders, has increased to include more than 20 distinct genetic syndromes. Studies of patients and mouse genetic models have indicated the important roles for lamins and their associated proteins in the function of gastrointestinal organs including liver and pancreas. We review the interactions and functions of the lamina in relation to the nuclear envelope and genome, the ways in which its dysfunction is thought to contribute to human disease, and possible avenues for targeted therapies.

Keywords

nucleoskeleton; envelopathies; progeria; myopathy; neuropathy; lipodystrophy; nonalcoholic fatty liver disease

In metazoan cells, a structural and functional link between the genome and the cytoskeleton is required to allow cells to quickly and appropriately respond to mechanical, chemical, inflammatory, and other stimuli. This link is provided by nuclear envelope proteins, which have collective and individual structural and regulatory roles. Nuclear pore complexes allow

[#]**To whom correspondence should be addressed:** University of Michigan Medical School, Division of Gastroenterology, Department of Internal Medicine, 1137 Catherine St., Ann Arbor, MI 48109-5622. gfbradv@med.umich.edu.

Disclosure(s): No potential conflicts of interest to report.

Author contributions: G.F.B., R.K., J.B.C., J.S.E., and M.B.O. jointly wrote the manuscript and generated the figures and tables.

regulated nuclear translocation of transcription factors and co-regulators[1]. The LINC complex (linker of the nucleoskeleton and cytoskeleton) tethers the nuclear envelope to cytoplasmic cytoskeletal networks, allowing transmission of mechanical and shear stress to the nucleus[2]. On the inner surface of the nuclear envelope, large regions of the genome, typically dominated by heterochromatin, are tethered to a multi-protein lattice[3, 4] (**Fig.1**). This complex of proteins, the nuclear lamina, lies beneath the inner nuclear membrane and physically associates with nuclear pore proteins and a variety of transmembrane and integral membrane proteins, and in direct contact with large portions of the genome.

The primary components of the nuclear lamina are lamins, which are type V intermediate filament proteins (IFs)—the most common IFs in the nucleus (although other IFs, such as keratins, are also found at lower levels in the nucleus)[5–8]. Lamins are encoded by 3 *genes* that generate the proteins: lamin A/C (*LMNA*; protein also referred to as LMNA), lamin B1 (*LMNB1*; protein also referred to as LMNB1), and lamin B2 (*LMNB2*; protein also referred to as LMNB2)[9–11]. The B-type lamins are expressed ubiquitously and throughout development, whereas A-type lamins are primarily expressed in differentiated cells[12, 13]. Together these proteins form a lattice that forms an interface with the inner nuclear membrane, nuclear pore complexes, transcription factors and co-regulatory proteins, and chromatin. Anchoring of the lamina to the inner nuclear membrane is achieved via B-type lamin farnesylation and lamin binding to transmembrane proteins that include lamina-associated polypeptide 1 (LAP1) and LEM-domain containing proteins such as LAP2β, emerin, and MAN1 (also called LEMD3)[14], whereas anchoring to the genome is thought to occur via adaptor proteins including barrier to autointegration factor (BANF1), the lamin B receptor (LBR), and direct binding of lamin to chromatin[15–18].

Lamin Post-translational Processing and Localization

Lamin C does not require post-translational modification to localize to the inner nuclear membrane. Lamin A, however, requires stepwise post-translational processing at the carboxy terminus via cysteine farnesylation at a cysteine-aliphatic-aliphatic-any amino acid (CAAX) motif, then proteolytic cleavage of the-AAX portion, carboxymethylation of the farnesylcysteine, and final clipping of the 15 carboxy-terminal residues, including the farnesylated cysteine, by the zinc metallopeptidase STE24 (ZMPSTE24)[19–22]. Although the B-type lamins are permanently farnesylated and found exclusively at the inner nuclear membrane as part of the nuclear lamina, a portion of LMNA is found in the nucleoplasm. Nucleoplasmic LMNA is stabilized by a mammal-specific isoform of thymopoietin (TMPO or LAP2), called LAP2a, but little is known about its function [23, 24]

Lamina-associated Proteins

A and B-type lamins form an intricate network of overlapping but independent 3-dimensional protein meshes[25] that interact with distinct subsets of the nuclear proteome. Lamin interactors include transmembrane LEM domain proteins such as LAP2β and MAN1, transcription factors such as SREBP1, transcriptional regulators including the RB transcriptional corepressor 1 (RB1), and adaptor proteins such as BANF1 that might facilitate chromatin binding to the lamina[15, 17, 26, 27] Two other critical nuclear envelope

structures mediate interactions between the nucleus and cytoplasm: nuclear pore complexes and the LINC complex. Nuclear pore complexes allow transcription factors, nuclear receptors, and signaling proteins to shuttle between the nucleus and cytoplasm[1]. A subset of nuclear pore complex proteins localizes to the nuclear periphery and/or with inactive regions of heterochromatin, whereas others are associated with active areas of euchromatin in the nuclear interior[28–30]. How this is regulated, and whether lamins or adaptor proteins such as BANF1 are involved, is unclear. Finally, the LINC complex[2] forms a key structural and regulatory connection between the nuclear envelope and the cytoskeleton, binding to nuclear lamins and the inner nuclear membrane on one side and actin filaments on the other (**Fig.1**).

Lamina-heterochromatin Interactions and Lamina-associated Domains

Several landmark studies have demonstrated the physical association between large regions of the genome (typically characterized by heterochromatin) and the nuclear lamina[3, 31–34] Some genomic regions—usually gene-poor, transcriptionally inactive regions—are associated with the lamina as part of lamina-associated domains (LADs) in numerous cell types, including pluripotent and terminally differentiated cells. In contrast, other regions of the genome may be found in or out of LADs depending on the cell type, or may move in and out of LADs during the process of cellular differentiation[3, 35]. For example, genomic regions associated with the lamina and transcriptionally silent in embryonic stem cells were found to dissociate from the lamina and become transcriptionally active during astrocyte differentiation[31]. Association with or dissociation from the nuclear lamina is therefore an important mechanism of transcriptional regulation during development; differential histone post-translational modification (methylation/acetylation) is likely to be involved in this process. Importantly, few studies have explored how disease-associated lamin variants affect organization of the genome and the LAD landscape in the involved tissues[36].

Lamina-related Diseases

Researchers began to realize that alterations in the nuclear lamina can lead to development of disease when genetic mapping and sequencing became widely available in the 1990s. In 1994, mutations in *EMD,* encoding emerin, an inner nuclear membrane protein, were found to cause X-linked Emery-Dreifuss muscular dystrophy (EDMD)[37]. Subsequently, autosomal mutations in *LMNA* were found to cause EDMD[38]. In the following years, many other monogenic diseases, called laminopathies and envelopathies, were attributed to mutations in lamins or their associated proteins, respectively (**Table 1**).

The laminopathies are characteristically syndromic and frequently have overlapping features. The pleiotropism of lamins and their associated proteins, combined with overlapping phenotypes, reflects their sophisticated regulation and diverse roles in many tissues[39]. Shared clinical features among laminopathies were initially interpreted as evidence of a single disease process with a spectrum of manifestations[40], but careful mapping of mutations revealed clear associations between mutations in distinct regions of the *LMNA* gene and different diseases[41]. For example, most patients with type 2 (Dunnigan) familial partial lipodystrophy (FPLD2) carry mutations in exons 7, 8, or 11 (UMD-LMNA mutations database [http://www.umd.be/LMNA]). Most of these mutations change the surface charge

of an immunoglobulin-like motif in LMNA, even though the overall integrity of the motif is maintained[42, 43]. Some patients with FPLD2 have additional findings consistent with limb-girdle muscular dystrophy (LGMD), whereas others with identical mutations are completely asymptomatic[44]. Intra-familial phenotypic differences, variable expressivity, and incomplete penetrance highlight the importance of undiscovered modifier genes that might serve as therapeutic targets.

Myopathies

Several striated myopathies are caused by mutations in genes encoding lamins or their associated proteins, characterized by dilated cardiomyopathy with variable skeletal muscle involvement, although disorders primarily involving smooth muscle have not been reported. The most common myopathic laminopathy resulting from mutations in *LMNA* and genes encoding other LAPs is EDMD, characterized by early contractures, progressive weakness, muscle wasting, and cardiomyopathy with conduction defects[45]. Distal (more so than proximal) muscle involvement and early neck, elbow, and achilles contractures in EDMD differentiate it from LGMD, which generally has more proximal muscle involvement and results from mutations in *LMNA* or *TOR1AIP1*[46, 47] Multiple clinically distinct cardiomyopathies have also been attributed to mutations in lamins and their associated proteins including dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, and Slovenian type heart-hand syndrome[48–50] (**Table 1**).

Progerias and developmental disorders

Hutchinson-Gilford progeria syndrome (HGPS) is perhaps the most well-recognized laminopathy because of its striking presentation of premature aging[51]. Classically, it is caused by a *de novo* point mutation activating a cryptic splice site in *LMNA* exon 11, generating truncated prelamin A that cannot be cleaved by ZMPSTE24 and remains farnesylated (resulting in a protein product called progerin), though other *LMNA* mutations can also cause HGPS[51–53]. Manifestations include alopecia, scleroderma, osteoporosis, lipodystrophy, atherosclerosis, and death within the first 2 decades of life[53]. Nestor-Guillermo progeria syndrome and progeria-like mandibuloacral dysplasia have also been attributed to mutations in genes encoding lamins or their associated proteins; these share features with other laminopathies including striated muscle defects and lipodystrophy[54, 55]. Restrictive dermopathy, caused by mutations in *LMNA* or *ZMPSTE24,* shares features with the progerias but is defined by tight skin resulting in the fetal hypokinesia sequence, including intrauterine growth retardation[56]. Other developmental disorders include Greenberg skeletal dysplasia and Buschke-Ollendorff syndrome, caused by mutations in *LBR* and *LEMD3,* respectively, with predominant skeletal phenotypes[57, 58].

Neuropathies and lipodystrophies

Numerous neuropathies have been linked to mutations in genes encoding lamins, including B-type lamins, and their associated proteins. For example, type 2B1 Charcot-Marie-Tooth disease (caused by *LMNA* mutation; **Table 1**) manifests as pes cavus with progressive sensory and motor neuropathy beginning in the lower extremities[59]. Mutations in *LMNB1* or *LMNB2* can cause a rare leukodystrophy or myoclonic dystrophy, respectively[60, 61].

Mutations in *LMNA* cause autosomal-dominant FPLD2[62–64], a fat storage disorder characterized by cushingoid appearance with decreased subcutaneous fat in the trunk and limbs, dyslipidemia, diabetes mellitus, and hepatic steatosis. Mutations in *LMNB2* predispose to acquired partial lipodystrophy, which shares many features with FPLD2[65].

Multifactorial diseases

Classical laminopathies are rare monogenic diseases, but there is mounting evidence that lamins and their associated proteins are also involved in more-common, multi-factorial disease processes. For example, lamin and nuclear pore complex dysfunction leads to neuronal cell death and modulates heterochromatin relaxation in Alzheimer disease[66, 67] There are conflicting data on whether defects in LMNA contribute to development of gastrointestinal cancers[68, 69] (**section 3.1**;**Table 2**); nuclear membrane-targeted gold particles can decrease tumor cell metastatic potential by increasing LMNA expression and nuclear stiffness[70]. A common variant of *LMNA* was reported as a risk factor for type 2 diabetes mellitus[71], and several LAPs were reported to be necessary for HIV-1 integration into nuclear chromatin in primary macrophages[72]. Continued advances in imaging and biochemical techniques will likely identify novel interactions within the nuclear lamina that lead to new disease associations.

Lamins and Associated Proteins in Gastrointestinal Diseases

Altered expression and/or localization of lamins and lamin-associated proteins has been associated with several gastrointestinal cancers[73, 74], although little is known about laminopathies that specifically affect gastrointestinal organs aside from the liver and pancreas[75–78]. What laminopathies affect the gastrointestinal tract, and what gastrointestinal diseases have been associated with lamina gene variants or altered expression/localization of nuclear lamina proteins?

Cancer

Malignant cells typically have changes in nuclear structure and morphology, such as altered protein composition and irregularly shaped nuclei[79–81], that resemble changes in cells that express mutant lamins or lamin-associated proteins. Altered expression and/or localization of lamins and their associated proteins has been reported in different types of gastrointestinal tumors (**Table 2**)[80, 81]. For example, levels of LMNA mRNA and protein were increased in esophageal adenocarcinoma specimens, compared to Barrett's esophagus with high-grade dysplasia[82]. However, another study showed that esophageal tumors (squamous and adenocarcinoma) had reduced expression of LMNA and LMNB1 compared to control esophageal tissue[73]. Levels of LMNA and LMNB1 were also reduced in gastric tumor and colon carcinoma and adenoma specimens, and were mislocalized to the cytoplasm in some colon carcinomas and adenomas[73, 74] In gastric adenocarcinoma, decreased LMNA expression correlated with poorly differentiated tumors and poor patient outcomes, compared to tumors that expressed normal levels of LMNA[74].

Findings from studies of colorectal cancer are contradictory. In a study of archived patient samples, tumor staining for LMNA correlated with decreased overall survival time of

patients, compared to samples that were negative for LMNA[69]. In another study, low LMNA expression was associated with increased recurrence among patients with stage II or III colon cancer[68]. This discrepancy may be related to the greater homogeneity of this cohort, which did not include patients with stage-I disease or rectal cancer[68] and/or the fact that in the former study, tumors with low and high levels of LMNA were grouped together as LMNA positive[69]. Notably, both studies used archived tissue samples and retrospective registry data; further study is needed to clarify the role of LMNA in colorectal cancer.

LMNB1 was consistently increased in liver tissues from patients with hepatocellular carcinoma (HCC) compared to patients without HCC[83, 84] Furthermore, increased levels of LMNB1 associated with larger tumors, increased number of tumor foci, and more advanced disease; *LMNB1* mRNA was increased in plasma from patients with HCC compared to individuals without HCC[51]. LMNB1 might therefore serve as a prognostic factor for patients with early-and late-stage HCC[83, 84]

Levels of lamin-associated and other nuclear proteins have also been examined in gastrointestinal tumors. For example, levels of LAP2α mRNA were increased in gastric and colon tumor tissues compared to non-tumor tissues[85]. Levels of BANF1 (protein and mRNA) were increased in esophageal squamous cell carcinoma, and high levels were associated with poor outcomes of patients[86]. Moreover, BANF1 mRNA and protein were increased in HCC samples compared to non-tumor liver tissues[87]. Notably, multiple heterozygous non-synonymous mutations in the spectrin repeat containing nuclear envelope protein 1 gene (SYNE1 or Nesp1) were identified in colorectal tumors[88], and SYNE1 was increased and mis-localized to the cytoplasm in duodenal and rectal tumors[89]. Nucleoporin 88 (NUP88), a nuclear pore complex protein, was highly expressed in HCC compared to non-tumor liver tissues, and overexpressed in colorectal tumors compared to non-tumor tissues. Levels of NUP88 increased during carcinogenesis and correlated with poorly differentiated tumors[90–92]. There is much evidence for alterations in lamins and their associated proteins in gastrointestinal tumors. Further studies are needed to determine the mechanisms of these changes and their potential role in tumor development, but they might be used as biomarkers of tumorigenesis or tumor progression.

Primary Biliary Cholangitis

Negative serologic results for anti-mitochondrial antibodies (AMA) present a challenge in the diagnosis of primary biliary cholangitis (PBC, previously called primary biliary cirrhosis). Antinuclear antibodies are present in sera from 25% of patients with PBC, and anti-LBR antibodies, along with anti-gp210 and anti-nucleoporin p62 autoantibodies, characterize a subset of PBC[93–95]. These autoantibodies produce a rim-like or membranous pattern that is highly specific for PBC and may represent a useful tool in the diagnosis of AMA-negative PBC[96–98]. Notably, Reynolds syndrome, characterized by concurrent scleroderma and PBC, was linked to an *LBR* missense variant in exon 9 (p.R372C), so it could be a previously unrecognized laminopathy[99] A systematic analysis of a large cohort of patients with PBC is necessary to validate *LBR* variants as a common cause of Reynolds syndrome[100].

Porphyria-associated liver injury

Porphyrias include 8 metabolic disorders of the heme biosynthetic pathway, each resulting from a specific enzyme defect, and are characterized by accumulation of heme precursors in diverse organs[101, 102]. Aggregation of LMNA and LMNB1 in the liver, a major site of heme synthesis, is an early marker of porphyria-associated liver injury in mice [102,103]. Furthermore, accumulation of porphyrin in HepG2 cells results in light-dependent aggregation of lamins and nuclear shape alterations[104], resembling the changes observed in patients with laminopathies. These nuclear alterations might affect transcription, via aggregate sequestration of lamins and other nuclear proteins[103,104].

Nonalcoholic fatty liver disease (NAFLD)

Hepatic steatosis, with progression to nonalcoholic steatohepatitis (NASH), is a common clinical feature of laminopathies including FPLD2 and other lipodystrophic syndromes and is considered a complication of these diseases[75, 105]. However, there is evidence that alterations in lamins and their associated proteins contribute to development of NAFLD and NASH, independent of lipodystrophy syndromes[76,77,106]. In a cohort of twin and sibling pairs with NAFLD (without lipodystrophy), coding sequence variants in lamina-related genes were identified in 90% of patients with NAFLD vs 36% of subjects without NAFLD[76]. Among these variants was an insertion in *TMPO* that causes a frameshift and insertion of a premature stop codon after amino acid 99 in all LAP2 isoforms. When expressed ectopically in human hepatoma cells, truncated LAP2 was mislocalized throughout the nucleus and cytoplasm, unable to bind LMNA, and altered the distribution of endogenous LMNA, LMB1, and LMNB2 in transfected cells. Cells expressing truncated LAP2 had greater lipid droplet accumulation than control cells (transfected with full-length LAP2α) after incubation with oleic acid[76]. Supporting these findings, hepatocyte-specific deletion of *LMNA* in mice altered growth hormone signaling via Jak and Stat proteins in hepatocytes and led to steatosis with progression to NASH with fibrosis (**section 4.6**)[77] It appears that patients with laminopathies are at greater risk for NAFLD or NASH due to hepatocyte-specific defects in LMNA; some cases of NAFLD or NASH might be associated with unrecognized laminopathies[75–77,107,108].

Insights From Animal Models

Our understanding of lamin function and the etiology of laminopathies has been greatly enhanced by the development of animal models. Mice with loss or gain of function alleles that are orthologous to human disease alleles recapitulate much of the tissue-specific features of human laminopathies. Phenotypic characterization of these mice has enabled the identification of physiologic abnormalities in affected tissues and alterations in signal transduction pathways and the transcriptome that contribute to pathogenesis. Mouse models of laminopathies have been useful in identifying agents that could alleviate disease symptoms and prolong life. What models of laminopathy have been developed and what have we learned about lamin function from these models (**Table 3**)?

B-type lamins

B-type lamins are expressed ubiquitously from early in embryonic development and regulate basic cellular functions such as senescence, replication, spindle assembly, chromatin organization, transcription, and resistance to oxidative stress[109–111]. It might be assumed, therefore, that mice lacking B-type lamins would die at an early stage of embryogenesis. In fact, mice with disruptions in *Lmnb1* and/or *Lmnb2* develop to term but die perinatally, with developmental defects in lung, bone, and brain[112–114]. Because Lmnb1 and Lmnb2 have 60% homology and similar expression patterns[115], functional redundancy could account for the relatively mild phenotype. However, $Lmnbl^{-/-}$ and $Lmnb2^{-/-}$ mice develop to term at the expected Mendelian frequency[113]. Moreover, combined tissue-specific deletion of *Lmnbl* and *Lmnb2* in keratinocytes and hepatocytes did not produce abnormal phenotypes or visible defects in tissue histology, nuclear shape, or cell proliferation[116, 117] These findings indicate that B-type lamins are not required for basic cellular functions but are required for the normal development of a subset of tissue types.

B-type lamins have important roles in brain development, based on defects in neuron migration and layering of forebrain neurons in $Lmnb1^{-/-}$ and $Lmnb2^{-/-}$ mice[112]. The similar phenotypes indicate that Lmnb1 and Lmnb2 have similar functions in brain. However, neuronal nuclei from $Lmnb1^{-/-}$ brains have a bleb-like structure, whereas those from $Lmnb2^{-/-}$ brains are elongated[112]. Moreover, differences in brain size and neuron numbers between these 2 lines indicate that Lmnb1 and Lmnb2 have distinct roles[112]. This finding was supported by studies in which the *Lmnb2* locus was replaced with *Lmnb1,* and vice versa. *Lmnb1* at the *Lmnb2* locus could not substitute for *Lmnb2,* and vice versa, resulting in brain phenotypes similar to those of $Lmnb1^{-/-}$ and $Lmnb2^{-/-}$ mice[115]. In addition, mice that express a nonfarnesylated form of Lmnb2 develop normally, as opposed to those that express nonfarnesylated Lmnb1, which die at birth with severe neurodevelopmental defects. These observations indicate different requirements in farnesylation for lamin function[118].

A-type lamins: Lmna loss of function alleles

The first strain of mice with a *LMNA* loss of function allele ($Lmna^{Sul}$) was generated via deletion of exons 8–11 of *Lmna*[119]. However, these mice express a truncated version of Lmna[120]. $Lmna^{Sul/Sul}$ mice have growth retardation at 2 weeks and die by 8 weeks of age. Death has been attributed to cachexia, muscular dystrophy, and cardiomyopathy. In embryonic fibroblasts from these mice, emerin mislocalized to the cytoplasm thereby indicating that $Lmna^{Sul/Sul}$ phenocopies EDMD (in which emerin expression is lost or the protein is mislocalized in myocytes)[119].

Two other strains of mice with loss of function alleles have been generated. These delete exons 2–12 of *Lmna*. Mice homozygous for these deletions have a similar phenotype mice homozygous for $Lmna^{Sul/Sul}$, but die by 3 weeks rather than 8 weeks of age, indicating that the truncated $Lmna^{Sul}$ gene product is partially functional[121, 122]

$Lmna^{Sul/Sul}$ mice were initially reported to have no adipogenic or metabolic defects[123]. However, subsequent studies with these mice[124], and with 2 separate lines of mice with

different loss of function alleles[121, 122], reported fat loss, impaired ex vivo adipogenesis, increased lipolysis in white adipose tissue, and impaired thermogenesis in brown adipose tissue in homozygous mice. *Lmna*$^{Sul/Sul}$ mice have a decrease in bone mass that correlates with significant reductions in numbers of osteoblast and osteocyte[119].

Studies of mice with a floxed allele that removes exons 10–12 of *Lmna* showed that LMNA, together with LBR, tethers peripheral heterochromatin to the nuclear envelope. In mice lacking LBR, loss of LMNA causes mislocalization of heterochromatin to the nuclear interior, with concomitant changes in gene expression and myocyte differentiation[125]. These studies indicate that lamin A/C is important for myocyte, osteocyte, and adipocyte differentiation and function, likely due to its role in regulating gene expression.

Lmna knock-in mice

Mouse models of laminopathies have been generated—these mice carry alleles orthologous to those that cause human laminopathies. Unlike in humans, in mice, most of these laminopathy alleles, especially those that cause muscular dystrophy and cardiomyopathy, are not fully penetrant in the heterozygous state or cause disease only in homozygous mice. Reasons for this recessive mode of inheritance are unclear[126]. Nevertheless, the homozygous mice develop phenotypes that are similar to human diseases and have provided important insights into the pathogenesis of laminopathies.

Progeroid Mouse Models

Mice that express progerin or a similar LMNA variant develop disorders similar to those of patients with HGPS (**Table 3**)[127,128,129]. These mice develop osteoporosis, kyphosis, alopecia, reduced subcutaneous fat, and cardiovascular disease and have a shortened lifespan[127–129]. Homozygous mice have a more severe phenotype than heterozygous mice, indicating that progerin levels determine the severity of disease[127–129].

Zmpste24$^{-/-}$ mice, which lack the metalloprotease required for processing prelamin A to mature lamin A, accumulate farnesylated prelamin A that remains attached to the inner nuclear membrane. These mice have a phenotype similar to that of progerin-expressing mice[19, 130], so accumulation of farnesylated lamin A might mediate the disease phenotype. In support of this hypothesis, decreasing *Lmna* dosage in *Zmpste24*$^{-/-}$mice using *Lmna*-null alleles reduces disease pathology[131]. Moreover, administration of a farnesyl transferase inhibitor (FTI) to *Zmpste24*$^{-/-}$ mice or progerin mice increased muscle strength and longevity and reduced rib fractures and the rate of weight loss[132,133]. The FTI did not fully rescue the progeria phenotype, however, and mice with a knock-in allele of non-farnesylated progerin were not completely protected from disease[128]. This indicates that the uncleaved C-termini in progerin and unprocessed prelamin A could also contribute to the disease phenotype, irrespective of farnesylation status. Mice that are engineered to express mature lamin A or C directly, bypassing prelamin A processing, have normal phenotypes, indicating that lamins A and C may be interchangeable[134,135]. Because lamin C does not require farnesylation or ZMPSTE24 proteolysis, increasing expression of lamin C, compared with lamin A, might a viable strategy for treating HGPS. A single copy of an allele that expresses only lamin C (*Lmna*^{LCO} mice) eliminates the progeria disease phenotype in *Zmpste24*$^{-/-}$

mice [135], and an antisense oligonucleotide that increases lamin C at the expense of prelamin A can reduce progeria-related cardiovascular disease in progerin mice[136]. So, strategies to reduce farnesylated prelamin A and progerin and/or increase lamin C expression might be developed for treatment of HGPS.

Models of Muscular Dystrophy and Cardiomyopathy

The H222P mutation in LMNA causes the autosomal-dominant form of EDMD. Mice homozygous for the orthologous mutation in *Lmna* develop muscular dystrophy and cardiomyopathy with heart chamber dilation, conduction defects, and cardiac fibrosis and die by 9 months of age[137]. Mice with a mutation in *Lmna* that causes the amino acid substitution N195K also develop dilated cardiomyopathy with conduction defects, but not muscular dystrophy; these mice die from cardiac arrhythmias by 3 months of age[138]. Mice with the H222P mutation in Lmna have become the primary model for studies of cardiomyopathy associated with defects of loss of this protein, because they have late onset of disease[139].

Transcriptome analysis of hearts from $Lmna^{H222P/H222P}$ mice indicates that dysregulation of signal transduction pathways contributes to disease pathology. Signal transduction pathways that are upregulated in $Lmna^{H222P/H222P}$ mice include the MAP kinase (ERK signaling to JNK and p38), Akt, and mTORC1 pathways[139]. MAP kinase inhibitors, of which the MEK inhibitors are the most extensively studied, have been shown to inhibit kinase activity in cardiac tissue, reduce the severity of disease, and improve heart function, indicating that constitutive activation of MAPK pathways is partly responsible for the disease phenotype[139]. However, it is unclear how MAPK hyperactivation occurs and how it contributes to disease progression.

mTORC1 is also hyperactivated in $Lmna^{H222P/H222P}$ as well as $Lmna^{Sul/Sul}$ hearts; mTORC1 activation correlates with decreased autophagy in both these lines of mice[140–143]. mTORC1 inhibitors increased autophagy and improved heart function in both lines of mice[140, 142], and the mTORC1 inhibitor rapamycin reversed metabolic defects in adipose tissue of $Lmna^{Sul/Sul}$ mice[124]. In $Lmna^{H222P/H222P}$ mice, the activator of mTORC1, AKT serine/threonine kinase 1 (AKT1), is hyperactivated, so H222P LMNA could hyperactivate mTORC1 through aberrant activation of AKT1, leading to decreased autophagy and cardiomyopathy[140]. Like AKT1, ERK is an activator of mTORC1; these could be involved in the mechanism by which MAPK hyperactivation in $Lmna^{H222P/H222P}$ mice promotes cardiomyopathy[140].

Based on transcriptome analysis, the Wnt pathway is also downregulated in $Lmna^{H222P/H222P}$ hearts, with reduced active and total β-catenin, Wnt, and Wnt10B proteins and increased frizzled-related proteins, which modulate the Wnt pathway[144]. Reductions in Wnt signaling were also noted in fibroblasts derived from progeroid $Lmna^{\Delta 9/\Delta 9}$ mice; this reduction appears to be responsible for the decrease in extracellular matrix production by mutant fibroblasts[145]. These data indicate that downregulation of Wnt signaling contributes to development of cardiomyopathy in $Lmna^{H222P/H222P}$ mice.

Role of LMNA in the Gastrointestinal Tract—Lessons From Mice

Tissue-or cell-specific and conditional disruption of *Lmna* is an important strategy for studying the role of LMNA in the gastrointestinal tract, given the severity of the phenotype in Lmna-deficient mice. *Lmna* has been disrupted in enterocytes, hepatocytes and acinar cells. In these cells, exons 10 and 11 of *Lmna* were removed using the Cre-lox system. Disruption of *Lmna* in enterocytes of mice using a Cre transgene under the control of the villin promoter did not alter gross morphology, lifespan, intestinal histology, or cell proliferation[146]. However, disruption of *Lmna* in enterocytes of $Apc^{Min/+}$ mice led to a slight increase in the total number of intestinal polyps, with as much as a 3-fold increase in the number of 2–5 mm polyps in the duodenum. These findings indicate that LMNA may act as a tumor suppressor[146–148].

In contrast to the modest phenotype resulting from disruption of *Lmna* in mouse enterocytes[146], hepatocyte-specific disruption of *Lmna* (using the same floxed allele as for enterocyte-specific disruption) reduces body mass but causes male-specific liver injury and steatosis that progresses to steatohepatitis and fibrosis in mice placed on a high-fat diet[77]. These changes correlated with upregulated transcription of genes that regulate lipogenesis, lipid transport, inflammation, type-1 interferon signaling, and fibrosis in mice on a standard diet; expression of genes that regulate fibrosis increases when mice are placed on a high-fat diet. The male specificity of the phenotype is likely due to defective growth hormone-mediated Jak2 signaling to Stat5. Activation of Stat5 regulates expression of male vs female sexually dimorphic genes in mouse livers[149–151]. Much like hepatocyte-specific disruption of *Stat5,* disruption of *Lmna* in hepatocytes leads to upregulation and constitutive activation of Stat1, which is necessary for inducible expression of type-1 interferon-regulated genes[152–154] and might contribute to inflammation in livers of mice.

Growth hormone-mediated activation of ERK was reduced in LMNA-deficient livers of mice, although it is not clear how this finding relates to the steatohepatitis phenotype of the mice. The defect in ERK activation is opposite to what is observed in $Lmna^{H222P/H222P}$ cardiomyocytes, in which ERK is hyperactivated do disrupt cardiac function[139, 155–157] The difference in the ERK phenotypes may be related to differences in the *Lmna* allele used, potential gain-of-function effects, and/or upstream pathways that are important in hepatocyte vs myocyte differentiation and function.

A major finding in the study of liver-specific LMNA-deficient mice is that disruption of *Lmna* leads to a cell-autonomous effect in hepatocytes to induce steatohepatitis. This result sheds a different light on the hypothesis that FPLD2-associated *LMNA* alleles cause lipodystrophy in humans primarily via effects on adipose tissue, with insulin resistance, metabolic syndrome, and NAFLD and NASH developing as secondary effects[158, 159] This adipose tissue-centric model is supported by results from mice that overexpress the FPLD2-associated LMNA R482Q in adipose tissue. These mice develop hepatic steatosis and impaired glucose tolerance compared with control mice that overexpress full-length LMNA[160]. However, a more recent study in which human LMNA R482Q was expressed in mouse adipose tissue at closer to physiologic levels demonstrated fibrosis in adipose tissue similar to human FPLD2, but no overt metabolic or hepatic phenotype[161]. Furthermore, a

recent abstract reported that deletion of TOR1AIP1 from hepatocytes of mice caused spontaneous steatosis and NASH, supporting the role of the hepatocyte nuclear envelope in steatohepatitis[162]. *Lmna* alleles might therefore act independently in adipocytes and hepatocytes to promote the FPLD2 phenotype. It should be noted, however, that human FPLD2 is caused by autosomal-dominant mutations in *LMNA* rather than loss of LMNA protein, and that men and women are affected, in contrast to the findings in mice after hepatocyte-specific disruption of *Lmna.* In addition, virtually all patients with FPLD2 and NAFLD or NASH are insulin resistant[75, 108]. Analysis of null and FPLD2 alleles of *Lmna* in adipocytes vs hepatocytes will be required to clarify the relative contributions of each cell type to the FPLD2 phenotype.

In the pancreas, inducible disruption of *Lmna* in acinar cells led to spontaneous pancreatitis, but only male mice developed chronic pancreatitis, based on increased Sirius-red and smooth muscle actin staining in knockout pancreata compared with controls[78]. Lmna-deficient pancreata from both sexes had smaller acini, smaller and fewer zymogen granules, decreased amylase expression, infiltration by inflammatory cells, and increased markers of endoplasmic reticulum stress, ductal cells, and cell proliferation[78]. These data indicate that acinar cell expression of LMNA is required for acinar cell homeostasis and that mutations that cause FPLD2 act in a cell-autonomous manner in acinar cells to promote FPLD2-related pancreatitis, which may also be precipitated by hypertriglyceridemia that is seen in some but not all patients[75]. Lmna deficiency in acinar cells also causes loss of Rb expression and concomitant activation of E2-factor F (E2F) transcription factors, based on the upregulated expression of E2F target genes[78]. A similar phenotype is observed in mice lacking the Lap2α, which regulates the E2F/Rb pathway as part of a complex with Lmna[23, 163]. Lap2α deficiency causes loss of nucleoplasmic Lmna and results in a hyperproliferative phenotype in mouse fibroblasts and epidermal and erythroid progenitor cells that has been attributed to loss of Rb-mediated E2F regulation[24].

Dysregulation of the Rb/E2F pathway is likely also responsible for the increased cell proliferation seen in the *Lmna*-deficient pancreatitis model. This phenotype counters what is observed in myoblasts from $Lmna^{Sul/Sul}$ mice, where *Lmna* deficiency leads to increased levels of Lap2α, Rb dephosphorylation and altered localization, and decreased cell proliferation[164]. Perhaps surprisingly, combined Lmna and Lap2α deficiency ($Lmna^{Sul/Sul}$; $Lap2\alpha^{-/-}$) rescues the $Lmna^{Sul/Sul}$ phenotype, increasing lifespan, body mass, and muscle cell proliferation[164]. Thus, the mechanisms by which LMNA and LAP2α regulate Rb and cell proliferation may vary with cell type.

Prospects for Therapy

Our increased understanding of lamin biology and the pathophysiology of laminopathies over the last several years has led to targeted therapeutic approaches—some have shown promise in preclinical studies, and there are limited but encouraging data from small clinical trials (**Fig.2**). Agents tested include farnesyl transferase inhibitors, which have extensive pre-clinical data to support their utility and have been studied in clinical trials; kinase inhibitors, which have been studied in models (and some are already used for treatment of diseases

unrelated to laminopathies); and small molecules designed to disrupt protein interactions or antisense oligonucleotide-based tools, which are in preclinical studies.

FTIs

FTIs have been studied in experimental models and clinical trials. In mouse models of HGPS, FTIs increased muscle strength, reduced weight loss and rib fractures, and increased lifespan[132, 133]. These agents have been tested in uncontrolled trials of children with HGPS. In a 25 children who received the FTI lonafarnib for at least 2 years, the primary outcome (>50% weight gain) was achieved by 9 patients (36%), whereas 10 patients (40%) maintained their pre-trial rates of weight gain during the study[165]. A pooled analysis of all patients with HGPS given an FTI, alone or in combination with zoledronate and pravastatin, showed significant increases in survival time with the FTI compared to without[166].

Kinase inhibition

Data from mouse models of laminopathies, particularly those affecting cardiac and skeletal muscle, indicate a role for aberrant MAP kinase and mTOR pathway activation (**section 4**). In *Lmna*$^{H222P/H222P}$ mice, administration of the MEK1/2 inhibitor selumetinib for 4 weeks inhibited ERK activation, prevented myocardial fibrosis, and prolonged survival[167]. Similar effects were observed when Lmna$^{H222P/H222P}$ mice were given other MEK1/2 inhibitors[156, 168], though these compounds have not yet advanced to trials of patients with *LMNA*-associated cardiomyopathy. in the *Lmna*$^{Sul/Sul}$ mice, rapamycin, an inhibitor of the mTOR pathway prolonged survival[124]. An open-label phase 1 and 2 trial of the mTOR inhibitor everolimus is underway, in combination with the FTI lonafarnib for HGPS (ClinicalTrials.gov Identifier: NCT02579044).

Other pre-clinical approaches

Based on transcriptomic data indicating alterations of Wnt signaling to β-catenin signaling in progeroid and *Lmna*$^{H222P/H222P}$ mice, these mice were given the Wnt activator 6-bromoindirubin-3'-oxime. This agent increased cardiac contractility and intraventricular conduction in these mice[144]. For progerin, given its binding to mature LMNA (but not LMNB1 or LMNB2) *in vitro*, screening a chemical library identified compounds capable of blocking the progerin-LMNA interaction[169]. One of these compounds improved nuclear morphology in progerin-overexpressing cells and HGPS patient-derived cells in culture, and improved weight gain, grip strength, and survival in progeroid mice.

An antisense oligonucleotide designed to alter splicing of *LMNA* mRNA to favor lamin C over prelamin A reduced production of progerin in fibroblasts derived from patients with HGPS. When this oligonucleotide was injected into wild-type C57BL/6J mice, it increased levels of lamin C and decreased lamin A, at the mRNA and protein levels, in liver. When injected into progeroid mice for 3-months, it decreased progerin and increased lamin C in aortic tissue and reduced aortic fibrosis[136].

Overview and Future Directions

Our understanding of the structure and function of lamins and lamina-associated proteins has expanded dramatically in the last 2 decades. Fundamental studies of the mechanistic details of lamin post-translational processing have allowed FTIs to be brought into clinical use for children with HGPS, with encouraging effects on weight gain and lifespan[165, 166] Similarly, based on extensive work in pre-clinical studies, kinase inhibitors hold promise for *LMNA*-related cardiomyopathies.

From the perspective of digestive health and disease, the effects of alterations to the nuclear lamina are becoming increasingly apparent. Gastrointestinal and hepatic manifestations of laminopathies that typically affect multiple organ systems, in addition to more recent data from mice and humans, have indicated the direct roles for lamins and their associated proteins[76–78].

Targeted therapies for lamina-related gastrointestinal disease are not yet on the horizon, although the observation that hepatocyte JAK2 signaling to STAT5 is defective in the absence of LMNA provides an avenue for investigation[77].

It is not clear why some *LMNA* mutations produce different phenotypes in different families, or even within the same family. It is likely that other genetic or environment factors and epigenetic differences determine how genotype affects phenotype—this is an important area for further study. Similarly, the relative contributions of environmental and genetic factors to common gastrointestinal conditions such as pancreatitis, and NAFLD, and NASH are unclear. We speculate that patients with such common diseases carry genetic variants that affect the nuclear lamina, without a clinically apparent laminopathy—a recent small study of twins and siblings with NAFLD supports this hypothesis[76]. As we move into the era of precision medicine, increasing our understanding of lamin biology and identifying disease-associated genetic variants lead to improved and targeted therapies that are even organ specific.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors wish to thank Drs. Roland Foisner and Howard Worman for their feedback and helpful comments pertaining to this review. We also thank all those who have provided biospecimens for the studies cited and who have participated in clinical studies to help improve our understanding and treatment of the involved diseases.

Financial Support: Our work is supported by National Institutes of Health (NIH) grants R01 DK47918 and R01 DK116548 (M.B.O.); American Liver Foundation (ALF) Liver Scholar Award (G.F.B.); and by an institutional grant (P30 DK034933) to the University of Michigan.

Abbreviations

AMA	anti-mitochondrial antibody
BANF1	barrier to autointegration factor

EDMD	Emery-Dreifuss muscular dystrophy
FTI	farnesyl transferase inhibitor
FPLD2	type 2 (Dunnigan) familial partial lipodystrophy
HCC	hepatocellular carcinoma
HGPS	Hutchinson-Gilford progeria syndrome
IF	intermediate filament proteins
LAD	lamina-associated domain
LAP	lamina-associated polypeptide
LEM	LAP2, emerin, MAN1
LGMD	limb-girdle muscular dystrophy
LINC	Linker of the Nucleoskeleton and Cytoskeleton
LMNA	lamin A/C
LMNB1	lamin B1
LMNB2	lamin B2
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
PBC	primary biliary cholangitis
Rb	retinoblastoma protein
SREBP1	sterol regulatory element-binding protein-1

References

1. Beck M, Hurt E. The nuclear pore complex: understanding its function through structural insight Nat Rev Mol Cell Biol. 2017; 18:73–89. [PubMed: 27999437]
2. Lee YL, Burke B. LINC complexes and nuclear positioning Semin Cell Dev Biol. 2017
3. Gonzalez-Sandoval A, Gasser SM. On TADs and LADs: Spatial Control Over Gene Expression Trends Genet. 2016; 32:485–95. [PubMed: 27312344]
4. Luperchio TR, Wong X, Reddy KL. Genome regulation at the peripheral zone: lamina associated domains in development and disease Curr Opin Genet Dev. 2014; 25:50–61. [PubMed: 24556270]
5. Hobbs RP, Jacob JT, Coulombe PA. Keratins Are Going Nuclear. Dev Cell. 2016; 38:227–33. [PubMed: 27505414]
6. Omary MB. “IF-pathies”: a broad spectrum of intermediate filament-associated diseases J Clin Invest. 2009; 119:1756–62. [PubMed: 19587450]
7. Butin-Israeli V, Adam SA, Goldman AE. Nuclear lamin functions and disease Trends Genet. 2012; 28:464–71. [PubMed: 22795640]
8. Burke B, Stewart CL. The nuclear lamins: flexibility in function Nat Rev Mol Cell Biol. 2013; 14:13–24. [PubMed: 23212477]

9. Lin F, Worman HJ. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C J Biol Chem. 1993; 268:16321–6. [PubMed: 8344919]
10. Lin F, Worman HJ. Structural organization of the human gene (LMNB1) encoding nuclear lamin B1 Genomics. 1995; 27:230–6. [PubMed: 7557986]
11. Biamonti G, Giacca M, Perini G. The gene for a novel human lamin maps at a highly transcribed locus of chromosome 19 which replicates at the onset of S-phase Mol Cell Biol. 1992; 12:3499–506. [PubMed: 1630457]
12. Stewart C, Burke B. Teratocarcinoma stem cells and early mouse embryos contain only a single major lamin polypeptide closely resembling lamin B Cell. 1987; 51:383–92. [PubMed: 3311384]
13. Rober RA, Weber K, Osborn M. Differential timing of nuclear lamin A/C expression in the various organs of the mouse embryo and the young animal: a developmental study Development. 1989; 105:365–78. [PubMed: 2680424]
14. Lin F, Blake DL, Callebaut I. MAN1, an inner nuclear membrane protein that shares the LEM domain with lamina-associated polypeptide 2 and emerin J Biol Chem. 2000; 275:4840–7. [PubMed: 10671519]
15. Haraguchi T, Koujin T, Segura-Totten M. BAF is required for emerin assembly into the reforming nuclear envelope J Cell Sci. 2001; 114:4575–85. [PubMed: 11792822]
16. Burke B, Stewart CL. Functional architecture of the cell's nucleus in development, aging, and disease Curr Top Dev Biol. 2014; 109:1–52. [PubMed: 24947235]
17. Margalit A, Segura-Totten M, Gruenbaum Y. Barrier-to-autointegration factor is required to segregate and enclose chromosomes within the nuclear envelope and assemble the nuclear lamina Proc Natl Acad Sci U S A. 2005; 102:3290–5. [PubMed: 15728376]
18. Stierle V, Couprie J, Ostlund C. The carboxyl-terminal region common to lamins A and C contains a DNA binding domain Biochemistry. 2003; 42:4819–28. [PubMed: 12718522]
19. Bergo MO, Gavino B, Ross J. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect Proc Natl Acad Sci U S A. 2002; 99:13049–54. [PubMed: 12235369]
20. Corrigan DP, Kuszczak D, Rusinol AE. Prelamin A endoproteolytic processing in vitro by recombinant Zmpste24 Biochem J. 2005; 387:129–38. [PubMed: 15479156]
21. Beck LA, Hosick TJ, Sinensky M. Isoprenylation is required for the processing of the lamin A precursor J Cell Biol. 1990; 110:1489–99. [PubMed: 2335559]
22. Weber K, Plessmann U, Traub P. Maturation of nuclear lamin A involves a specific carboxy-terminal trimming, which removes the polyisoprenylation site from the precursor; implications for the structure of the nuclear lamina FEBS Lett. 1989; 257:411–4. [PubMed: 2583287]
23. Dechat T, Korbei B, Vaughan OA. Lamina-associated polypeptide 2alpha binds intranuclear A-type lamins J Cell Sci. 2000; 19:113–84. 3473.
24. Naetar N, Korbei B, Kozlov S. Loss of nucleoplasmic LAP2alpha-lamin A complexes causes erythroid and epidermal progenitor hyperproliferation Nat Cell Biol. 2008; 10:1341–8. [PubMed: 18849980]
25. Turgay Y, Eibauer M, Goldman AE. The molecular architecture of lamins in somatic cells Nature. 2017; 543:261–264. [PubMed: 28241138]
26. Zastrow MS, Vlcek S, Wilson KL. Proteins that bind A-type lamins: integrating isolated clues J Cell Sci. 2004; 117:979–87. [PubMed: 14996929]
27. Ozaki T, Saijo M, Murakami K. Complex formation between lamin A and the retinoblastoma gene product: identification of the domain on lamin A required for its interaction Oncogene. 1994; 9:2649–53. [PubMed: 8058329]
28. Pascual-Garcia P, Debo B, Aleman JR. Metazoan Nuclear Pores Provide a Scaffold for Poised Genes and Mediate Induced Enhancer-Promoter Contacts Mol Cell. 2017; 66:63–76 e6. [PubMed: 28366641]
29. Capelson M, Liang Y, Schulte R. Chromatin-bound nuclear pore components regulate gene expression in higher eukaryotes Cell. 2010; 140:372–83. [PubMed: 20144761]
30. Raices M, D'Angelo MA. Nuclear pore complexes and regulation of gene expression Curr Opin Cell Biol. 2017; 46:26–32. [PubMed: 28088069]

31. Perovanovic J, Dell'Orso S, Gnochi VF. Laminopathies disrupt epigenomic developmental programs and cell fate Sci Transl Med. 2016; 8:335ra58.
32. Finlan LE, Sproul D, Thomson I. Recruitment to the nuclear periphery can alter expression of genes in human cells PLoS Genet. 2008; 4:e1000039. [PubMed: 18369458]
33. Reddy KL, Zullo JM, Bertolino E. Transcriptional repression mediated by repositioning of genes to the nuclear lamina Nature. 2008; 452:243–7. [PubMed: 18272965]
34. Zullo JM, Demarco IA, Pique-Regi R. DNA sequence-dependent compartmentalization and silencing of chromatin at the nuclear lamina Cell. 2012; 149:1474–87. [PubMed: 22726435]
35. Peric-Hupkes D, Meuleman W, Pagie L. Molecular maps of the reorganization of genome-nuclear lamina interactions during differentiation Mol Cell. 2010; 38:603–13. [PubMed: 20513434]
36. Paulsen J, Sekelja M, Oldenburg AR. Chrom3D: three-dimensional genome modeling from Hi-C and nuclear lamin-genome contacts Genome Biol. 2017; 18:21. [PubMed: 28137286]
37. Bione S, Maestrini E, Rivella S. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy Nat Genet. 1994; 8:323–7. [PubMed: 7894480]
38. Bonne G, Di Barletta MR, Varnous S. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy Nat Genet. 1999; 21:285–8. [PubMed: 10080180]
39. Mercuri E, Poppe M, Quinlivan R. Extreme variability of phenotype in patients with an identical missense mutation in the lamin A/C gene: from congenital onset with severe phenotype to milder classic Emery-Dreifuss variant Arch Neurol. 2004; 61:690–4. [PubMed: 15148145]
40. Capell BC, Collins FS. Human laminopathies: nuclei gone genetically awry Nat Rev Genet. 2006; 7:940–52. [PubMed: 17139325]
41. McKenna, T., Baek, J-H., Eriksson, M. Laminopathies, Genetic Disorders, Prof.Maria, Puiu (Ed.), InTech. 2013.
42. Dhe-Paganon S, Werner ED, Chi YI. Structure of the globular tail of nuclear lamin J Biol Chem. 2002; 277:17381–4. [PubMed: 11901143]
43. Krimm I, Ostlund C, Gilquin B. The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy Structure. 2002; 10:811–23. [PubMed: 12057196]
44. Vigouroux C, Magre J, Vantyghem MC. Lamin A/C gene: sex-determined expression of mutations in Dunnigan-type familial partial lipodystrophy and absence of coding mutations in congenital and acquired generalized lipoatrophy Diabetes. 2000; 49:1958–62. [PubMed: 11078466]
45. Bonne G, Mercuri E, Muchir A. Clinical and molecular genetic spectrum of autosomal dominant Emery-Dreifuss muscular dystrophy due to mutations of the lamin A/C gene Ann Neurol. 2000; 48:170–80. [PubMed: 10939567]
46. Kayman-Kurekci G, Talim B, Korkusuz P. Mutation in TOR1AIP1 encoding LAP1B in a form of muscular dystrophy: a novel gene related to nuclear envelopathies Neuromuscul Disord. 2014; 24:624–33. [PubMed: 24856141]
47. Muchir A, Bonne G, van der Kooi AJ. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B) Hum Mol Genet. 2000; 9:1453–9. [PubMed: 10814726]
48. Fatkin D, MacRae C, Sasaki T. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease N Engl J Med. 1999; 341:1715–24. [PubMed: 10580070]
49. Merner ND, Hodgkinson KA, Haywood AF. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene Am J Hum Genet. 2008; 82:809–21. [PubMed: 18313022]
50. Renou L, Stora S, Yaou RB. Heart-hand syndrome of Slovenian type: a new kind of laminopathy J Med Genet. 2008; 45:666–71. [PubMed: 18611980]
51. Eriksson M, Brown WT, Gordon LB. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome Nature. 2003; 423:293–8. [PubMed: 12714972]
52. Goldman RD, Shumaker DK, Erdos MR. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome Proc Natl Acad Sci U S A. 2004; 101:8963–8. [PubMed: 15184648]

53. De Sandre-Giovannoli A, Bernard R, Cau P. Lamin a truncation in Hutchinson-Gilford progeria Science. 2003; 300:2055. [PubMed: 12702809]
54. Agarwal AK, Fryns JP, Auchus RJ. Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia Hum Mol Genet. 2003; 12:1995–2001. [PubMed: 12913070]
55. Puente XS, Quesada V, Osorio FG. Exome sequencing and functional analysis identifies BANF1 mutation as the cause of a hereditary progeroid syndrome Am J Hum Genet. 2011; 88:650–6. [PubMed: 21549337]
56. Navarro CL, De Sandre-Giovannoli A, Bernard R. Lamin A. ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy Hum Mol Genet. 2004; 13:2493–503. [PubMed: 15317753]
57. Hellemans J, Preobrazhenska O, Willaert A. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis Nat Genet. 2004; 36:1213–8. [PubMed: 15489854]
58. Waterham HR, Koster J, Mooyer P. Autosomal recessive HEM/Greenberg skeletal dysplasia is caused by 3 beta-hydroxysterol delta 14-reductase deficiency due to mutations in the lamin B receptor gene Am J Hum Genet. 2003; 72:1013–7. [PubMed: 12618959]
59. De Sandre-Giovannoli A, Chaouch M, Kozlov S. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth disorder type 2) and mouse Am J Hum Genet. 2002; 70:726–36. [PubMed: 11799477]
60. Damiano JA, Afawi Z, Bahlo M. Mutation of the nuclear lamin gene LMNB2 in progressive myoclonus epilepsy with early ataxia Hum Mol Genet. 2015; 24:4483–90. [PubMed: 25954030]
61. Padiath QS, Saigoh K, Schiffmann R. Lamin B1 duplications cause autosomal dominant leukodystrophy Nat Genet. 2006; 38:1114–23. [PubMed: 16951681]
62. Cao H, Hegele RA. Nuclear lamin A/C R482Q mutation in canadian kindreds with Dunnigan-type familial partial lipodystrophy Hum Mol Genet. 2000; 9:109–12. [PubMed: 10587585]
63. Shackleton S, Lloyd DJ, Jackson SN. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy Nat Genet. 2000; 24:153–6. [PubMed: 10655060]
64. Speckman RA, Garg A, Du F. Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C Am J Hum Genet. 2000; 66:1192–8. [PubMed: 10739751]
65. Hegele RA, Cao H, Liu DM. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy Am J Hum Genet. 2006; 79:383–9. [PubMed: 16826530]
66. Frost B, Bardai FH, Feany MB. Lamin Dysfunction Mediates Neurodegeneration in Tauopathies Curr Biol. 2016; 26:129–36. [PubMed: 26725200]
67. Sheffield LG, Miskiewicz HB, Tannenbaum LB. Nuclear pore complex proteins in Alzheimer disease J Neuropathol Exp Neurol. 2006; 65:45–54. [PubMed: 16410748]
68. Belt EJ, Fijneman RJ, van den Berg EG. Loss of lamin A/C expression in stage II and III colon cancer is associated with disease recurrence Eur J Cancer. 2011; 47:1837–45. [PubMed: 21621406]
69. Willis ND, Cox TR, Rahman-Casans SF. Lamin A/C is a risk biomarker in colorectal cancer PLoS One. 2008; 3:e2988. [PubMed: 18714339]
70. Ali MRK, Wu Y, Ghosh D. Nuclear Membrane-Targeted Gold Nanoparticles Inhibit Cancer Cell Migration and Invasion ACS Nano. 2017; 11:3716–3726. [PubMed: 28333438]
71. Wegner L, Andersen G, Sparso T. Common variation in LMNA increases susceptibility to type 2 diabetes and associates with elevated fasting glycemia and estimates of body fat and height in the general population: studies of 7,495 Danish whites Diabetes. 2007; 56:694–8. [PubMed: 17327437]
72. Jacque JM, Stevenson M. The inner-nuclear-envelope protein emerin regulates HIV-1 infectivity Nature. 2006; 441:641–5. [PubMed: 16680152]
73. Moss SF, Krivosheyev V, de Souza A. Decreased and aberrant nuclear lamin expression in gastrointestinal tract neoplasms Gut. 1999; 45:723–9. [PubMed: 10517909]

74. Wu Z, Wu L, Weng D. Reduced expression of lamin A/C correlates with poor histological differentiation and prognosis in primary gastric carcinoma J Exp Clin Cancer Res. 2009; 28:8. [PubMed: 19144202]
75. Ajluni N, Meral R, Neidert AH. Spectrum of disease associated with partial lipodystrophy: lessons from a trial cohort Clin Endocrinol (Oxf). 2017; 86:698–707. [PubMed: 28199729]
76. Brady GF, Kwan R, Ulintz PJ. Nuclear lamina genetic variants, including a truncated LAP2, in twins and siblings with nonalcoholic fatty liver disease Hepatology. 2018; in press. doi: 10.1002/hep.29522
77. Kwan R, Brady GF, Brzozowski M. Hepatocyte-Specific Deletion of Mouse Lamin A/C Leads to Male-Selective Steatohepatitis Cell Mol Gastroenterol Hepatol. 2017; 4:365–383. [PubMed: 28913408]
78. Elenbaas JS, Bragazzi Cunha J, Azuero-Dajud R. Lamin A/C maintains exocrine pancreas homeostasis by regulating stability of RB and activity of E2F Gastroenterology. 2018; in press. doi: 10.1053/j.gastro.2018.01.024
79. Zwerger M, Ho CY, Lammerding J. Nuclear mechanics in disease Annu Rev Biomed Eng. 2011; 13:397–428. [PubMed: 21756143]
80. Denais C, Lammerding J. Nuclear mechanics in cancer Adv Exp Med Biol. 2014; 773:435–70. [PubMed: 24563360]
81. Sakthivel KM, Sehgal P. A Novel Role of Lamins from Genetic Disease to Cancer Biomarkers Oncol Rev. 2016; 10:309. [PubMed: 27994771]
82. Zhao J, Chang AC, Li C. Comparative proteomics analysis of Barrett metaplasia and esophageal adenocarcinoma using two-dimensional liquid mass mapping Mol Cell Proteomics. 2007; 6:987–99. [PubMed: 16829691]
83. Sun S, Xu MZ, Poon RT. Circulating Lamin B1 (LMNB1) biomarker detects early stages of liver cancer in patients J Proteome Res. 2010; 9:70–8. [PubMed: 19522540]
84. Lim SO, Park SJ, Kim W. Proteome analysis of hepatocellular carcinoma Biochem Biophys Res Commun. 2002; 291:1031–7. [PubMed: 11866469]
85. Parise P, Finocchiaro G, Masciadri B. Lap2alpha expression is controlled by E2F and deregulated in various human tumors Cell Cycle. 2006; 5:1331–41. [PubMed: 16760672]
86. Li J, Wang T, Pei L. Expression of VRK1 and the downstream gene BANF1 in esophageal cancer Biomed Pharmacother. 2017; 89:1086–1091. [PubMed: 28298069]
87. Shen Q, Eun JW, Lee K. BANF1, PLOD3, SF3B4 as Early-stage Cancer Decision Markers and Drivers of Hepatocellular Carcinoma Hepatology. 2018; in press. doi: 10.1002/hep.29606
88. Sjoblom T, Jones S, Wood LD, Parsons DW. The consensus coding sequences of human breast and colorectal cancers Science. 2006; 314:268–74. [PubMed: 16959974]
89. Liggett JL, Choi CK, Donnell RL. Nonsteroidal anti-inflammatory drug sulindac sulfide suppresses structural protein Nesprin-2 expression in colorectal cancer cells Biochim Biophys Acta. 2014; 1840:322–31. [PubMed: 24080406]
90. Knoess M, Kurz AK, Goreva O. Nucleoporin 88 expression in hepatitis B and C virus-related liver diseases World J Gastroenterol. 2006; 12:5870–4. [PubMed: 17007055]
91. Zhang ZY, Zhao ZR, Jiang L. Nup88 expression in normal mucosa, adenoma, primary adenocarcinoma and lymph node metastasis in the colorectum Tumour Biol. 2007; 28:93–9. [PubMed: 17264541]
92. Xu S, Powers MA. Nuclear pore proteins and cancer Semin Cell Dev Biol. 2009; 20:620–30. [PubMed: 19577736]
93. Toh BH. Diagnostic autoantibodies for autoimmune liver diseases Clin Transl Immunology. 2017; 6:e139. [PubMed: 28690845]
94. Duarte-Rey C, Bogdanos D, Yang CY. Primary biliary cirrhosis and the nuclear pore complex Autoimmun Rev. 2012; 11:898–902. [PubMed: 22487189]
95. Courvalin JC, Lassoued K, Worman HJ. Identification and characterization of autoantibodies against the nuclear envelope lamin B receptor from patients with primary biliary cirrhosis J Exp Med. 1990; 172:961–7. [PubMed: 2167346]

96. Nickowitz RE, Wozniak RW, Schaffner F. Autoantibodies against integral membrane proteins of the nuclear envelope in patients with primary biliary cirrhosis Gastroenterology. 1994; 106:193–9. [PubMed: 8276182]

97. Muratori P, Muratori L, Ferrari R. Characterization and clinical impact of antinuclear antibodies in primary biliary cirrhosis Am J Gastroenterol. 2003; 98:431–7. [PubMed: 12591064]

98. Granito A, Muratori P, Muratori L. Antinuclear antibodies giving the 'multiple nuclear dots' or the 'rim-like/membranous' patterns: diagnostic accuracy for primary biliary cirrhosis Aliment Pharmacol Ther. 2006; 24:1575–83. [PubMed: 17206945]

99. Gaudy-Marqueste C, Roll P, Esteves-Vieira V. LBR mutation and nuclear envelope defects in a patient affected with Reynolds syndrome J Med Genet. 2010; 47:361–70. [PubMed: 20522425]

100. Cabane J. Is Reynolds syndrome a genetic laminopathy? Gastroenterol Clin Biol. 2010; 34:509–10. [PubMed: 20800400]

101. Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment Blood. 2012; 120:4496–504. [PubMed: 22791288]

102. Puy H, Gouya L, Deybach JC. Porphyrias Lancet. 2010; 375:924–37. [PubMed: 20226990]

103. Singla A, Griggs NW, Kwan R. Lamin aggregation is an early sensor of porphyria-induced liver injury J Cell Sci. 2013; 126:3105–12. [PubMed: 23641075]

104. Maitra D, Elenbaas JS, Whitesall SE. Ambient Light Promotes Selective Subcellular Proteotoxicity after Endogenous and Exogenous Porphyrinogenic Stress J Biol Chem. 2015; 290:23711–24. [PubMed: 26205816]

105. Guenantin AC, Briand N, Bidault G. Nuclear envelope-related lipodystrophies Semin Cell Dev Biol. 2014; 29:148–57. [PubMed: 24384368]

106. Dutour A, Roll P, Gaborit B. High prevalence of laminopathies among patients with metabolic syndrome Hum Mol Genet. 2011; 20:3779–86. [PubMed: 21724554]

107. Hendrikx T, Schnabl B. Lamin Deficiency in the Liver Sets the Stage for Nonalcoholic Steatohepatitis Development in Males Cell Mol Gastroenterol Hepatol. 2017; 4:441–442. [PubMed: 29062878]

108. Ludtke A, Genschel J, Brabant G. Hepatic steatosis in Dunnigan-type familial partial lipodystrophy Am J Gastroenterol. 2005; 100:2218–24. [PubMed: 16181372]

109. Dechat T, Adam SA, Taimen P. Nuclear lamins Cold Spring Harb Perspect Biol. 2010; 2:a000547. [PubMed: 20826548]

110. Freund A, Laberge RM, Demaria M. Lamin B1 loss is a senescence-associated biomarker Mol Biol Cell. 2012; 23:2066–75. [PubMed: 22496421]

111. Shimi T, Butin-Israeli V, Adam SA. The role of nuclear lamin B1 in cell proliferation and senescence Genes Dev. 2011; 25:2579–93. [PubMed: 22155925]

112. Coffinier C, Jung HJ, Nobumori C. Deficiencies in lamin B1 and lamin B2 cause neurodevelopmental defects and distinct nuclear shape abnormalities in neurons Mol Biol Cell. 2011; 22:4683–93. [PubMed: 21976703]

113. Kim Y, Sharov AA, McDole K. Mouse B-type lamins are required for proper organogenesis but not by embryonic stem cells Science. 2011; 334:1706–10. [PubMed: 22116031]

114. Vergnes L, Peterfy M, Bergo MO. Lamin B1 is required for mouse development and nuclear integrity Proc Natl Acad Sci U S A. 2004; 101:10428–33. [PubMed: 15232008]

115. Lee JM, Jung HJ, Fong LG. Do lamin B1 and lamin B2 have redundant functions? Nucleus. 2014; 5:287–92. [PubMed: 25482116]

116. Yang SH, Jung HJ, Coffinier C. Are B-type lamins essential in all mammalian cells? Nucleus. 2011; 2:562–9. [PubMed: 22127257]

117. Yang SH, Chang SY, Yin L. An absence of both lamin B1 and lamin B2 in keratinocytes has no effect on cell proliferation or the development of skin and hair Hum Mol Genet. 2011; 20:3537–44. [PubMed: 21659336]

118. Jung HJ, Nobumori C, Goulbourne CN. Farnesylation of lamin B1 is important for retention of nuclear chromatin during neuronal migration Proc Natl Acad Sci U S A. 2013; 110:E1923–32. [PubMed: 23650370]

119. Sullivan T, Escalante-Alcalde D, Bhatt H. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy J Cell Biol. 1999; 147:913–20. [PubMed: 10579712]
120. Jahn D, Schramm S, Schnolzer M. A truncated lamin A in the Lmna −/− mouse line: implications for the understanding of laminopathies Nucleus. 2012; 3:463–74. [PubMed: 22895093]
121. Kim Y, Zheng Y. Generation and characterization of a conditional deletion allele for Lmna in mice Biochem Biophys Res Commun. 2013; 440:8–13. [PubMed: 23998933]
122. Kubben N, Voncken JW, Konings G. Post-natal myogenic and adipogenic developmental: defects and metabolic impairment upon loss of A-type lamins Nucleus. 2011; 2:195–207. [PubMed: 21818413]
123. Cutler DA, Sullivan T, Marcus-Samuels B. Characterization of adiposity and metabolism in Lmna-deficient mice Biochem Biophys Res Commun. 2002; 291:522–7. [PubMed: 11855819]
124. Liao CY, Anderson SS, Chicoine NH. Rapamycin Reverses Metabolic Deficits in Lamin A/C-Deficient Mice Cell Rep. 2016; 17:2542–2552. [PubMed: 27926859]
125. Solovei I, Wang AS, Thanisch K. LBR and lamin A/C sequentially tether peripheral heterochromatin and inversely regulate differentiation Cell. 2013; 152:584–98. [PubMed: 23374351]
126. Stewart CL. Mouse models of the nuclear envelopathies and related diseases. Preface Curr Top Dev Biol. 2014; 109:xi–xiii. [PubMed: 24947241]
127. Osorio FG, Navarro CL, Cadinanos J. Splicing-directed therapy in a new mouse model of human accelerated aging Sci Transl Med. 2011; 3:106ra107.
128. Yang SH, Andres DA, Spielmann HP. Progerin elicits disease phenotypes of progeria in mice whether or not it is farnesylated J Clin Invest. 2008; 118:3291–300. [PubMed: 18769635]
129. Mounkes LC, Kozlov S, Hernandez L. A progeroid syndrome in mice is caused by defects in A-type lamins Nature. 2003; 423:298–301. [PubMed: 12748643]
130. Pendas AM, Zhou Z, Cadinanos J. Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice Nat Genet. 2002; 31:94–9. [PubMed: 11923874]
131. Fong LG, Ng JK, Meta M. Heterozygosity for Lmna deficiency eliminates the progeria-like phenotypes in Zmpste24-deficient mice Proc Natl Acad Sci U S A. 2004; 101:18111–6. [PubMed: 15608054]
132. Fong LG, Frost D, Meta M. A protein farnesyltransferase inhibitor ameliorates disease in a mouse model of progeria Science. 2006; 311:1621–3. [PubMed: 16484451]
133. Yang SH, Meta M, Qiao X. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation J Clin Invest. 2006; 116:2115–21. [PubMed: 16862216]
134. Coffinier C, Jung HJ, Li Z. Direct synthesis of lamin A, bypassing prelamin a processing, causes misshapen nuclei in fibroblasts but no detectable pathology in mice J Biol Chem. 2010; 285:20818–26. [PubMed: 20439468]
135. Fong LG, Ng JK, Lammerding J. Prelamin A and lamin A appear to be dispensable in the nuclear lamina J Clin Invest. 2006; 116:743–52. [PubMed: 16511604]
136. Lee JM, Nobumori C, Tu Y. Modulation of LMNA splicing as a strategy to treat prelamin A diseases J Clin Invest. 2016; 126:1592–602. [PubMed: 26999604]
137. Arimura T, Helbling-Leclerc A, Massart C. Mouse model carrying H222P-Lmna mutation develops muscular dystrophy and dilated cardiomyopathy similar to human striated muscle laminopathies Hum Mol Genet. 2005; 14:155–69. [PubMed: 15548545]
138. Mounkes LC, Kozlov SV, Rottman JN. Expression of an LMNA-N195K variant of A-type lamins results in cardiac conduction defects and death in mice Hum Mol Genet. 2005; 14:2167–80. [PubMed: 15972724]
139. Muchir A, Worman HJ. Targeting Mitogen-Activated Protein Kinase Signaling in Mouse Models of Cardiomyopathy Caused by Lamin A/C Gene Mutations Methods Enzymol. 2016; 568:557–80. [PubMed: 26795484]
140. Choi JC, Muchir A, Wu W. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation Sci Transl Med. 2012; 4:144ra102.

141. Choi JC, Worman HJ. Reactivation of autophagy ameliorates LMNA cardiomyopathy Autophagy. 2013; 9:110–1. [PubMed: 23044536]
142. Ramos FJ, Chen SC, Garelick MG. Rapamycin reverses elevated mTORC1 signaling in lamin A/C-deficient mice, rescues cardiac and skeletal muscle function, and extends survival Sci Transl Med. 2012; 4:144ra103.
143. Ramos FJ, Kaeberlein M, Kennedy BK. Elevated MTORC1 signaling and impaired autophagy Autophagy. 2013; 9:108–9. [PubMed: 23064282]
144. Le Dour C, Macquart C, Sera F. Decreased WNT/beta-catenin signalling contributes to the pathogenesis of dilated cardiomyopathy caused by mutations in the lamin a/C gene Hum Mol Genet. 2017; 26:333–343. [PubMed: 28069793]
145. Hernandez L, Roux KJ, Wong ES. Functional coupling between the extracellular matrix and nuclear lamina by Wnt signaling in progeria Dev Cell. 2010; 19:413–25. [PubMed: 20833363]
146. Wang AS, Kozlov SV, Stewart CL. Tissue specific loss of A-type lamins in the gastrointestinal epithelium can enhance polyp size Differentiation. 2015; 89:11–21. [PubMed: 25578479]
147. Moser AR, Pitot HC, Dove WF. A dominant mutation that predisposes to multiple intestinal neoplasia in the mouse Science. 1990; 247:322–4. [PubMed: 2296722]
148. Su LK, Kinzler KW, Vogelstein B. Multiple intestinal neoplasia caused by a mutation in the murine homolog of the APC gene Science. 1992; 256:668–70. [PubMed: 1350108]
149. Clodfelter KH, Holloway MG, Hodor P. Sex-dependent liver gene expression is extensive and largely dependent upon signal transducer and activator of transcription 5b (STAT5b): STAT5b-dependent activation of male genes and repression of female genes revealed by microarray analysis Mol Endocrinol. 2006; 20:1333–51. [PubMed: 16469768]
150. Holloway MG, Cui Y, Laz EV. Loss of sexually dimorphic liver gene expression upon hepatocyte-specific deletion of Stat5a-Stat5b locus Endocrinology. 2007; 148:1977–86. [PubMed: 17317776]
151. Udy GB, Towers RP, Snell RG. Requirement of STAT5b for sexual dimorphism of body growth rates and liver gene expression Proc Natl Acad Sci U S A. 1997; 94:7239–44. [PubMed: 9207075]
152. Cui Y, Hosui A, Sun R. Loss of signal transducer and activator of transcription 5 leads to hepatosteatosis and impaired liver regeneration Hepatology. 2007; 46:504–13. [PubMed: 17640041]
153. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses Nat Rev Immunol. 2014; 14:36–49. [PubMed: 24362405]
154. Tassiulas I, Hu X, Ho H. Amplification of IFN-alpha-induced STAT1 activation and inflammatory function by Syk and ITAM-containing adaptors Nat Immunol. 2004; 5:1181–9. [PubMed: 15467722]
155. Muchir A, Pavlidis P, Decostre V. Activation of MAPK pathways links LMNA mutations to cardiomyopathy in Emery-Dreifuss muscular dystrophy J Clin Invest. 2007; 117:1282–93. [PubMed: 17446932]
156. Muchir A, Shan J, Bonne G. Inhibition of extracellular signal-regulated kinase signaling to prevent cardiomyopathy caused by mutation in the gene encoding A-type lamins Hum Mol Genet. 2009; 18:241–7. [PubMed: 18927124]
157. Muchir A, Wu W, Worman HJ. Mitogen-activated protein kinase inhibitor regulation of heart function and fibrosis in cardiomyopathy caused by lamin A/C gene mutation Trends Cardiovasc Med. 2010; 20:217–21. [PubMed: 22293021]
158. Huang-Doran I, Sleigh A, Rochford JJ. Lipodystrophy: metabolic insights from a rare disorder J Endocrinol. 2010; 207:245–55. [PubMed: 20870709]
159. Lee PL, Tang Y, Li H. Raptor/mTORCl loss in adipocytes causes progressive lipodystrophy and fatty liver disease Mol Metab. 2016; 5:422–32. [PubMed: 27257602]
160. Wojtanik KM, Edgemon K, Viswanadha S. The role of LMNA in adipose: a novel mouse model of lipodystrophy based on the Dunnigan-type familial partial lipodystrophy mutation J Lipid Res. 2009; 50:1068–79. [PubMed: 19201734]

161. Le Dour C, Wu W, Bereziat V. Extracellular matrix remodeling and transforming growth factor-beta signaling abnormalities induced by lamin A/C variants that cause lipodystrophy J Lipid Res. 2017; 58:151–163. [PubMed: 27845687]

162. Shin J-Y, Hernandez-Ono A, Fedotova T. Novel mouse model of nonalcoholic steatohepatitis Hepatology. 2017; 66:1079A.

163. Dorner D, Vlcek S, Foeger N. Lamina-associated polypeptide 2alpha regulates cell cycle progression and differentiation via the retinoblastoma-E2F pathway J Cell Biol. 2006; 173:83–93. [PubMed: 16606692]

164. Cohen TV, Gnocchi VF, Cohen JE. Defective skeletal muscle growth in lamin A/C-deficient mice is rescued by loss of Lap2alpha Hum Mol Genet. 2013; 22:2852–69. [PubMed: 23535822]

165. Gordon LB, Kleinman ME, Miller DT. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome Proc Natl Acad Sci U S A. 2012; 109:16666–71. [PubMed: 23012407]

166. Gordon LB, Massaro J, D'Agostino RB Sr.. Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome Circulation. 2014; 130:27–34. [PubMed: 24795390]

167. Muchir A, Reilly SA, Wu W. Treatment with selumetinib preserves cardiac function and improves survival in cardiomyopathy caused by mutation in the lamin A/C gene Cardiovasc Res. 2012; 93:311–9. [PubMed: 22068161]

168. Wu W, Chordia MD, Hart BP. Macrocyclic MEK1/2 inhibitor with efficacy in a mouse model of cardiomyopathy caused by lamin A/C gene mutation Bioorg Med Chem. 2017; 25:1004–1013. [PubMed: 28011205]

169. Lee SJ, Jung YS, Yoon MH. Interruption of progerin-lamin A/C binding ameliorates Hutchinson-Gilford progeria syndrome phenotype J Clin Invest. 2016; 126:3879–3893. [PubMed: 27617860]

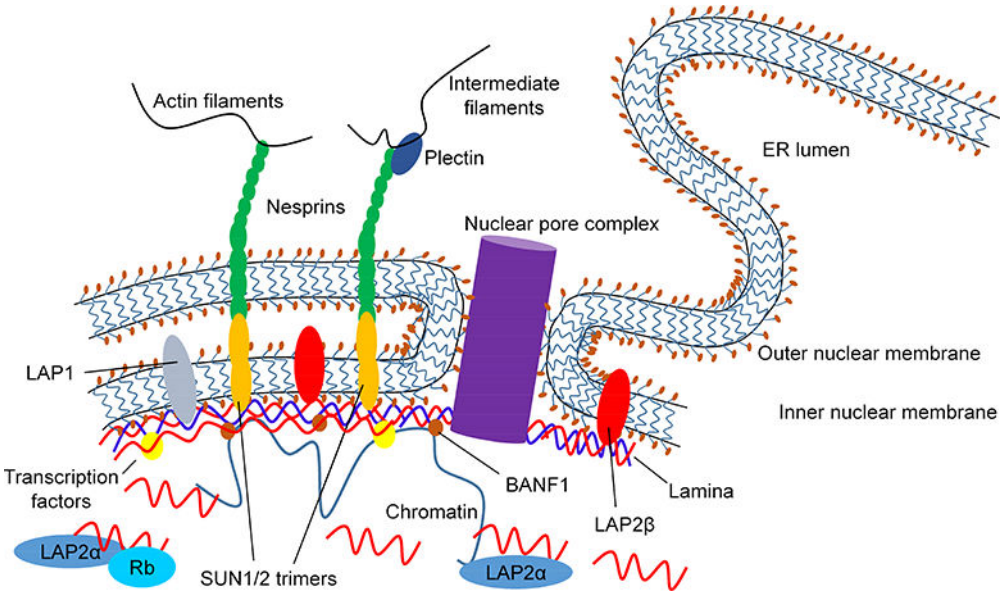

Figure 1.

Structure of the nuclear envelope including nuclear pore complex, LINC complex, and the nuclear lamina. Schematic of the nuclear envelope structure including outer and inner nuclear membranes, the lamina, integral membrane proteins, nuclear pore complex, LINC complexes, components of the cytoplasmic cytoskeleton, and chromatin-lamina contacts. The outer nuclear membrane is shown in continuity with the membrane of the endoplasmic reticulum (ER). A portion of LMNA (red) is shown as a soluble nucleoplasmic protein, some of which is bound to LAP2α.

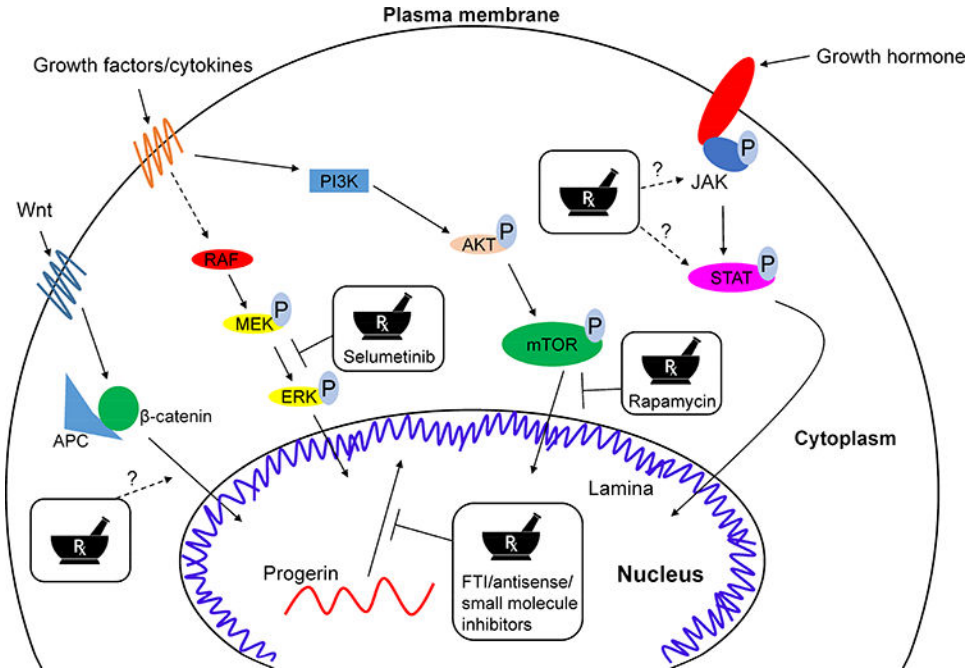

Figure 2.

Affected pathways in laminopathies and potential avenues for therapeutic intervention. Alterations in multiple pathways contribute to the pathogenesis of laminopathies. Strategies tested in preclinical or clinical studies are indicated with solid arrows. Strategies to alter Wnt signaling to β-catenin or growth hormone signaling via Jak and Stat proteins, which are altered in mouse models of laminopathies but have not been tested in animal models or clinical trials, are indicated with dashed arrows. Agents developed to reduce or block activity of progerin, FTIs[132,133,165,166], antisense oligonucleotides[136], and small molecules that inhibit progerin interaction with LMNA[169] have been tested.

Table 1:

Human diseases linked to mutations in genes encoding lamins and associated proteins. **Key: A-type lamins | B-type lamins | Lamin associated proteins | Lamin processing proteins**

Disease [references]	Gene (Phenotype MIM number)	Phenotype
	LMNA (181350, 616516)	
Emery-Dreifuss muscular dystrophy [37,38,S1–3]	*EMD* (310300) *SYNE1* (612998) *SYNE2* (612999) *TMEM43* (614302)	Skeletal myopathy, cardiomyopathy, early contractures, cardiac conduction defects
Limb girdle muscular dystrophy [46,47]	*LMNA* (159001) *TOR1AIP1* (617072)	Progressive limb weakness, late contractures, arrhythmogenic cardiomyopathy
Muscular dystrophy, congenital [39]	*LMNA* (613205)	Limb and axial muscle weakness and wasting
Dilated cardiomyopathy, type 1A [48,S4]	*LMNA* (115200)	Cardiac dilation, reduced ejection fraction
Cardiomyopathy, dilated, with hypergonadotropic hypogonadism [S5]	*LMNA* (212112)	Cardiomyopathy, hypogonadism
Heart-hand syndrome, Slovenian type [50]	*LMNA* (610140)	Heart conduction defects, cardiomyopathy, abnormal bone development in hands and feet
Hutchinson-Gilford progeria syndrome [51,53]	*LMNA* (176670)	Symptoms of premature ageing, alopecia, scleroderma, lipodystrophy, cardiovascular defects
Restrictive dermopathy [56,S6]	*LMNA* (275210) *ZMPSTE24* (275210)	Taut facies, intrauterine growth retardation, death within weeks of extrauterine life
Mandibuloacral dysplasia [54,S7]	*LMNA* (248370) *ZMPSTE24* (608612)	Mandibular hypoplasia, growth restriction, progressive osteolysis, variable lipodystrophy and progeroid symptoms.
Charcot-Marie-Tooth disease, type 2B1 [59,S8]	*LMNA* (605588)	Lower limb motor and sensory neuropathy, pes cavus
Familial partial lipodystrophy, type 2 [62–64]	*LMNA* (151660)	Abnormal distribution of subcutaneous fat with cushingoid appearance, metabolic defects including diabetes mellitus and hypertriglyceridemia
Leukodystrophy, adult-onset, autosomal dominant [61]	*LMNB1* (169500)	Multiple-sclerosis-like symptoms, autonomic dysfunction, CNS demyelination
Progressive myoclonic epilepsy-9 [60]	*LMNB2* (616540)	Myoclonic epilepsy, brain developmental defects, muscle atrophy
Lipodystrophy, partial, acquired, susceptibility to [65]	*LMNB2* (608709)	Loss of subcutaneous fat, metabolic disorder
Nestor-Guillermo progeria syndrome [55]	*BANF1* (614008)	Variable lipoatrophy, skeletal and cardiac abnormalities
Greenberg skeletal dysplasia [58]	*LBR* (215140)	Osteochondroplasia, fetal demise, hydrops
Pelger-Huet anomaly [S9]	*LBR* (169400)	Skeletal defects, epilepsy, developmental delay, abnormal granulocyte nuclear morphology
Buschke-Ollendorff syndrome [57]	*LEMD3* (166700)	Multiple nevi, osteopoikilosis
Spinocerebellar ataxia, autosomal recessive 8 [S1]	*SYNE1* (610743)	Ataxia, dysarthria, variable muscle atrophy
Deafness, autosomal recessive 76 [S10]	*SYNE4* (615540)	Progressive high-frequency hearing loss
Arrhythmogenic right ventricular dysplasia 5 [49]	*TMEM43* (604400)	Arrhythmogenic cardiomyopathy, right ventricular dysplasia, center ventricular enlargement

Table 2:

Changes in lamins and associated proteins in human gastrointestinal cancers. Key: **A-type lamins | B-type lamins | Lamin associated proteins**

Cancer	Gene	Finding [references]	Clinical significance
Esophageal adenocarcinoma	*LMNA*	Upregulation (protein & mRNA) [82] Downregulation (protein) [73]	Unknown
	LMNB1	Downregulation (protein) [73]	Unknown
Esophageal squamous cell carcinoma	*LMNA*	Downregulation (protein) [73]	Unknown
	LMNB1	Downregulation (protein) [73]	Unknown
	BANF1	Upregulation (protein & mRNA) [86]	Poor prognosis
Gastric adenocarcinoma	*LMNA*	Downregulation (protein & mRNA) [73,74]	Poorly differentiated tumors, poor prognosis
	LMNB1	Downregulation (protein) [73]	Unknown
	TMPO	Upregulated (mRNA) [85]	Unknown
	SYNE2	Upregulation, mislocalization (protein) [89]	Unknown
Duodenal and rectal adenocarcinoma	*LMNA*	Positive staining [69] Low expression (protein) [68]	Poor prognosis Increased risk of recurrence
	LMNA/LMNB1	Downregulation, mislocalization (protein) [73,74]	Unknown
Colorectal adenocarcinoma	*TMPO*	Upregulation (mRNA) [85]	Unknown
	SYNE1	Non-synonymous variants [88]	Unknown
	NUP88	Upregulation (protein) [92	Unknown
	LMNB1	Upregulation (protein & plasma mRNA) [83,84]	Larger tumor size and number, more advanced disease; potential biomarker
Hepatocellular carcinoma	*BANF1*	Upregulation (protein & mRNA) [87]	Putative early biomarker of HCC
	NUP88	Upregulation (protein) [90,91]	Poorly differentiated tumors; increased expression during carcinogenesis

Table 3:

Mouse models of lamin-related disease.

Mouse model [references]	Disease Relevance/Affected Tissues	Model design	Model phenotype
LMNA$^{Sul/Sul}$[119,124,143,164,811]	DCM, EDMD, FPLD2/ Striated muscle, bone, liver, pancreas, adipose tissue	*LMNA* exons 8 through top of exon 11 deleted	Reduced growth from 2–3 weeks of age; abnormal gait and posture, muscular dystrophy, decreased bone mass, cardiomyopathy, reduced subcutaneous fat (lethal by 8 weeks of age)
LMNA$^{GT-/-}$ [122]	DCM, EDMD, FPLD2/ Striated muscle, adipose tissue	Gene trap insertion in *LMNA* intron 2	Reduced growth, abnormal gait, muscle weakness, cardiomyopathy, reduced subcutaneous fat, lethal by postembryonic day 16–18 (P16-P18)
LMNA$^{flx/flx}$ CMV-Cre [121]	DCM, EDMD, FPLD2/ Striated muscle, adipose tissue	LoxP sites flanking *LMNA* exon 2, CMV-Cre drives whole-body *LMNA* deletion	Similar to *LMNA*$^{Sul/Sul}$ and *LMNA*$^{GT-/-}$ models; lethal by P16-P18
LMNA$^{flx/flx}$; Zp3-Cre [125]	DCM, EDMD, FPLD2/ Striated muscle, adipose tissue	LoxP sites flanking *LMNA* exons 10–11, Zp3-Cre drives whole-body *LMNA* deletion	Phenotype not described; lethal between P13-P18
LMNA$^{69/69}$ [129,145]	HGPS Skin, bone, adipose tissue	*LMNA* L530P; alternative splicing generates truncated protein that remains farnesylated.	Subcutaneous fat loss, osteoporosis, abnormal dentition, thin skin, growth retardation, and shortened lifespan
LMNA$^{G609G/G609G}$ [127]	HGPS Skin, bone, adipose tissue	*LMNA* G609G; cryptic splice site results in loss of Zmpste24 cleavage site and expression of progerin	Subcutaneous fat loss, alopecia, reduced bone density, kyphosis, thymic and splenic atrophy, reduced lifespan
LMNA$^{HG/+}$ [128]	HGPS Skin, bone, adipose tissue	*LMNA* introns 10–11, part of exon 11 removed; loss of Zmpste24 cleavage site and expression of progerin	Heterozygotes exhibited slow weight gain, rib fractures, loss of body fat, reduced lifespan
LMNA$^{nHG/+}$ [128]	HGPS Skin, bone, adipose tissue	Same as *LMNA*$^{HG/+}$ except CAAX mutated to SAAX; non-farnesylated progerin expressed	Heterozygotes exhibited slow weight gain, rib fractures, loss of body fat, and shortened lifespan (less severe *LMNA*$^{nHG/+}$)
Zmpste24$^{-/-}$ (Pendas) [130]	HGPS Skin, bone, adipose tissue	*Zmpste24*$^{-/-}$ exons 2–3 deleted	Weight loss, kyphosis, muscle weakness, alopecia; average lifespan of 20 weeks
Zmpste24$^{-/-}$ (Bergo) [19]	HGPS Skin, bone, adipose tissue	*Zmpste24*$^{-/-}$ exon 8 deleted	Spontaneous fractures, slow weight gain, alopecia, kyphosis, muscle weakness, average lifespan of 6–7 months
LMNA$^{LCO/LCO}$ [135]	HGPS	*LMNA* intron 11, part of exon 11 removed; lamin C but not prelamin A produced	Homozygotes similar to WT
LMNA$^{LAO/LAO}$ [134]	HGPS	*LMNA* introns 10–11, first 24 bp of exon 12 removed; mature lamin A expressed, not prelamin A or lamin C	Homozygotes similar to WT
H222P *LMNA* [137,139,155,156]	DCM and EDMD Striated muscle	*LMNA* H222P (causes EDMD in humans)	Kyphosis, shallow breathing, dilated cardiomyopathy, reduced lifespan; no lipodystrophy
N195K *LMNA* [138]	DCM Cardiac muscle	*LMNA* N195K (causes DCM in humans)	Cardiac muscle degeneration, dilated heart chambers, conduction defects; lethal by 12–14 weeks of age

Mouse model [references]	Disease Relevance/Affected Tissues	Model design	Model phenotype
LMNA$^{flx/flx}$; Villin-Cre [146]	Intestinal epithelium	LoxP sites flanking *LMNA* exons 10–11, Villin-Cre drives *LMNA* deletion in intestinal epithelial cells	Slight increase in number of intestinal polyps with *Apc*$^{Min/+}$ background
LMNA$^{flx/flx}$; Alb-Cre [77]	FPLD2 and NAFLD Liver	LoxP sites flanking *LMNA* exons 10–11, Alb-Cre drives *LMNA* deletion in hepatocytes	Male-specific liver injury and steatosis, with steatohepatitis and fibrosis after high fat diet
LMNA$^{flx/flx}$; Cela1-CreERT2 [78]	Pancreas	LoxP sites flanking *LMNA* exons 10–11, Cela1-CreERT2 drives inducible *LMNA* deletion in acinar cells	ER stress, increased apoptosis and proliferation, chronic pancreatitis, fibrosis
R482Q *LMNA* transgenic mice [160,161]	FPLD2 Adipose tissue	*LMNA* (human) R482Q transgene	Weight plateau at 41 weeks, fat pad loss, hepatic steatosis, thermogenesis defects, adipocyte differentiation defects [160]; TGF-β activation and fibrosis in adipose tissue [161]
Lap2α$^{-/-}$ [24,S12–13]	DCM Striated muscle, epidermal/erythroid progenitor cells	*Tmpo/Lap2* exon 4 deleted, eliminates Lap2α expression, preserves other isoforms	Systolic dysfunction, cardiac fibrosis in older mice, hyperproliferation of epidermal and erythroid progenitor cells
Lmnb1$^{-/-}$ (Kim) [113]	Lung, diaphragm, brain	*Lmnb1* exon 1 deleted	Delayed embryonic growth, lung/diaphragm defects, microencephaly, respiratory failure, perinatal lethality
Lmnb1$^{\Delta/\Delta}$ [112,114]	Lung, bone, brain	Gene trap cassette in *Lmnb1* intron 5; protein lacks NLS and CAAX motif	Abnormal lung development and bone ossification, microencephaly, respiratory failure, perinatal lethality
Lmnb2$^{-/-}$ (Kim) [113]	Diaphragm, brain	*Lmnb2* exon 1 deleted	Brain and diaphragm defects, respiratory failure, perinatal lethality
Lmnb2$^{-/-}$ (Coffinier) [112]	Brain	*Lmnb2* exon 1 replaced with lacZ reporter	Abnormal layering of cortical neurons in cerebral cortex, perinatal lethality
Lmnb1$^{-/-}$; *Lmnb2*$^{-/-}$ (Kim) [113]	Lung, diaphragm, brain	*Lmnb1*, *Lmnb2* loci deleted	Thin diaphragm, microencephaly, delayed embryonic growth, perinatal lethality
*Lmnb1*f *Lmnb2*$^{flx/flx}$; Emx1-Cre [112]	Forebrain	LoxP sites flanking exon 2 of *Lmnb1* and *Lmnb2*, Emx1-Cre drives forebrain-specific deletion	Cortical atrophy, loss of hippocampal structures, perinatal lethality
Lmnb1$^{flx/flx}$; *Lmnb2*$^{flx/flx}$; K14-Cre [117]	Skin	LoxP sites flanking exon 2 of *Lmnb1* and *Lmnb2*, K14-Cre drives keratinocyte-specific deletion	Normal skin and hair, normal keratinocyte proliferation
Lmnb1$^{flx/flx}$; *Lmb2*$^{flx/flx}$; Alb-Cre [116]	Liver	LoxP sites flanking exon 2 of Lmnb1 and *Lmnb2*, Alb-Cre drives hepatocyte-specific deletion	Similar to WT; liver chemistries and histology normal
Lmnb1$^{B2/B2}$[115,S14]	Brain	Lmnb1 locus replaced with *Lmnb2*	Cortical neuron layering defect, decreased body mass (less severe than *Lmnb1*$^{-/-}$)
Lmnb2$^{B1/B1}$ [115,S14]	Brain	*Lmnb2* locus replaced with Lmnb1	Normal body mass, slightly decreased brain size, cortical neuron layering defect
Lmnb1$^{CS/CS}$ [118]	Lung, brain	Lmnb1 CAAX motif replaced with SAAX	Cortical layering defect, microencephaly, lung defects, perinatal lethality

Mouse model [references]	Disease Relevance/Affected Tissues	Model design	Model phenotype
Lmnb2$^{CS/CS}$ [118]	Brain	*Lmnb2* CAAX motif replaced with SAAX	Similar to WT (normal growth, fertility, lifespan)