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Current insights into *LMNA* cardiomyopathies: Existing models and missing LINC

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ABSTRACT

The nuclear lamina is a critical structural domain for the maintenance of genomic stability and whole-cell mechanics. Mutations in the *LMNA* gene, which encodes nuclear A-type lamins lead to the disruption of these key cellular functions, resulting in a number of devastating diseases known as laminopathies. Cardiomyopathy is a common laminopathy and is highly penetrant with poor prognosis. To date, cell mechanical instability and dysregulation of gene expression have been proposed as the main mechanisms driving cardiac dysfunction, and indeed discoveries in these areas have provided some promising leads in terms of therapeutics. However, important questions remain unanswered regarding the role of lamin A dysfunction in the heart, including a potential role for the toxicity of lamin A precursors in *LMNA* cardiomyopathy, which has yet to be rigorously investigated.

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Introduction

LMNA encodes the intermediate filament proteins lamins A and C which are generated by alternative splicing.¹ While lamin C is translated as a mature protein, lamin A is translated as a precursor, prelamin A, and requires extensive C-terminal processing to reach maturation. The B-type lamins are generated from 2 genes B1 from the *LMNB2* gene, and B2 and B3 from *LMNB3*.² A-type lamins polymerise into high order lattice structures with the B-type lamins to form the nuclear lamina (NL). The NL lies directly adjacent to the inner nuclear membrane (INM) on the nucleoplasmic side and forms a physical complex with SUN domain proteins and nesprins, which together comprise the nuclear envelope (NE) spanning Linkers of the Nucleoskeleton to Cytoskeleton (LINC) complex.³ On the cytoplasmic face of the outer nuclear membrane (ONM) nesprins link to cytoskeletal components, predominantly F-actin, and provide a structural link between the nucleus and cytoplasm.⁴ This structural link can be viewed as reaching as far as the extracellular matrix (ECM) if the sequential links between F-actin and focal adhesion proteins are considered. This tethering of the lamina with NE spanning proteins via the LINC complex is crucial for the

integrity of whole-cell mechanics, as well as mechanotransduction to the nucleus from the cytoplasmic and extracellular domains.⁵

Inside the nucleus, lamins associate with LEM proteins (LAP2, Emerin, MAN) and heterochromatin.⁶ They serve a scaffolding function in order to facilitate the correct expression of genes as well as enable efficient DNA damage repair. When the integrity of the NL is compromised, these processes become dysregulated with potentially devastating results. Patients harbouring mutations in *LMNA* can develop a number of different tissue-specific syndromes collectively termed laminopathies, many of which can be broadly defined as 'premature aging disorders' and include Hutchinson Gilford progeria syndrome (HGPS). One of the most common diseases caused by *LMNA* mutations is cardiomyopathy, which can occur as an isolated phenotype or frequently in combination with a skeletal muscle dystrophy such as Emery Dreifuss muscular dystrophy (EDMD) or limb girdle muscular dystrophy.^{7–10} It has also been described in parallel with a number of other laminopathies (Table 1).^{11–16}

Two key processes have been proposed to account for cardiac dysfunction. **The mechanical hypothesis** proposes that disruption to and uncoupling of structural

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Table 1. Laminopathies identified to have overlapping cardiomyopathy phenotypes.

Laminopathy	Heart involvement	Ref
Dilated cardiomyopathy with conduction defects	Left ventricle dilatation, systolic dysfunction, atrioventricular conduction block, arrhythmia, congestive heart failure	7
Emery Dreifuss muscular dystrophy	Atrioventricular conduction block, arrhythmia, systolic dysfunction, congestive heart failure	8,9
Limb girdle muscular dystrophy	Atrioventricular block, progressive left ventricle dysfunction, arrhythmia	10
Variant progeroid syndrome with right ventricular cardiomyopathy	Right atrium and ventricle dilatation, tricuspid valve dilatation	11
Atypical progeroid syndrome with cardiomyopathy	Right ventricle dilatation, arrhythmia, tricuspid valve regurgitation	11,12
Familial partial lipodystrophy of dunningan type 2	Left ventricle dilatation, systolic dysfunction, atrioventricular block, complete left bundle branch block	13
Lipodystrophy with hypertrophic cardiomyopathy	Left ventricle hypertrophy, aortic valve calcification, stenosis and regurgitation	15
Charcot Marie Tooth type 2 axonal neuropathy	Left ventricle dilatation, systolic dysfunction,	15
Severe metabolic syndrome*	Left ventricle dilatation, systolic dysfunction, ventricular extra systole	16

*Caused by a *ZMPSTE24* mutation

proteins at the NL leads to increased pathologic susceptibility to mechanical stress. Consequently, tissues that endure high levels of mechanical stress, i.e. striated muscle and heart, are most susceptible to disease. The **gene expression hypothesis** implies that structural changes to the NL not only lead to impaired transduction of signals from the extracellular and cytoplasmic domains, but also disrupted chromatin organization which impacts directly on gene transcription. However, the molecular events immediately downstream of lamin dysfunction are not well understood, especially in the context of the whole organ. Moreover these 2 mechanisms are unlikely to be mutually exclusive (Fig. 1), so it is not clear which, if either, is the key trigger. Importantly, the mechanisms that promote premature aging associated with accumulation of lamin A variants, such as increased levels of DNA damage and senescence, as observed in other tissues, have not been studied in the context of *LMNA* induced cardiomyopathy. This review explores the role of A-type nuclear lamins in the context of the clinical features of cardiomyopathies caused by mutations in *LMNA* and discusses the body of knowledge regarding pathologic mechanisms, and future areas for development.

Cardiomyopathy

Cardiomyopathies are characterized by cardiomyocyte (CM) dysfunction and tissue-wide remodelling of the

myocardium leading to functional decline.¹⁷ They are mainly caused by familial mutations in structural proteins, but are also caused by somatic *de novo* mutations or external causes such as myocarditis,^{18,19} toxin exposure,²⁰ chemotherapy²¹ and autoimmunity.²² They also arise due to age related changes to the vasculature leading to pressure overload of the heart. Cardiomyopathies eventually progress to heart failure, the point at which the heart is no longer able to pump sufficient blood through the body to meet the metabolic demands of the respiring tissues (Fig. 2).

Cardiomyopathies are classified according to their functional and morphological features.²³ The foremost classifications are dilated- (DCM), hypertrophic- (HCM) and arrhythmogenic right ventricular- (ARVC).²⁴

Dilated cardiomyopathy

DCM is characterized by dilation of one, or both, ventricular chambers. Functionally, it is accompanied by reduced force of contraction leading to reduced cardiac output. Structurally, DCM is characterized by ventricular wall thinning, resulting from cardiomyocyte death and myocardial fibrosis. DCM can be caused by mutations in genes encoding proteins of the sarcomere, sarcolemma desmosome and NE. Upwards of 40 disease genes have been identified, most of which are autosomal dominant mutations.²⁵

DCM mechanisms can be categorised into mechanical dysfunction, structural dysfunction and dysregulation of Ca^{2+} handling. In mechanical dysfunction mutations in genes encoding sarcomeric proteins such as β myosin heavy chain (β -MHC), reduce contractility whereas mutations in genes encoding actin thin filaments cause a reduction in Ca^{2+} sensitivity by attenuating the affinity of myofilaments to calcium, resulting in reduced generation of force in the myocyte. Structural deficiencies are caused by mutations in genes encoding cytoskeletal components, and include proteins of the sarcomere and the costamere, which links the sarcomere to the sarcolemma and ECM.²⁶⁻²⁸ Mutations also occur in intermediate filament proteins such as desmin, which link the sarcomere to the cell periphery and also to the nucleus via the LINC complex (Fig. 3).²⁹ Disrupting any one of these compartments inhibits transmission of force throughout the myocyte. Dysregulation of Ca^{2+} handling is caused by mutations in *PLN*, the gene

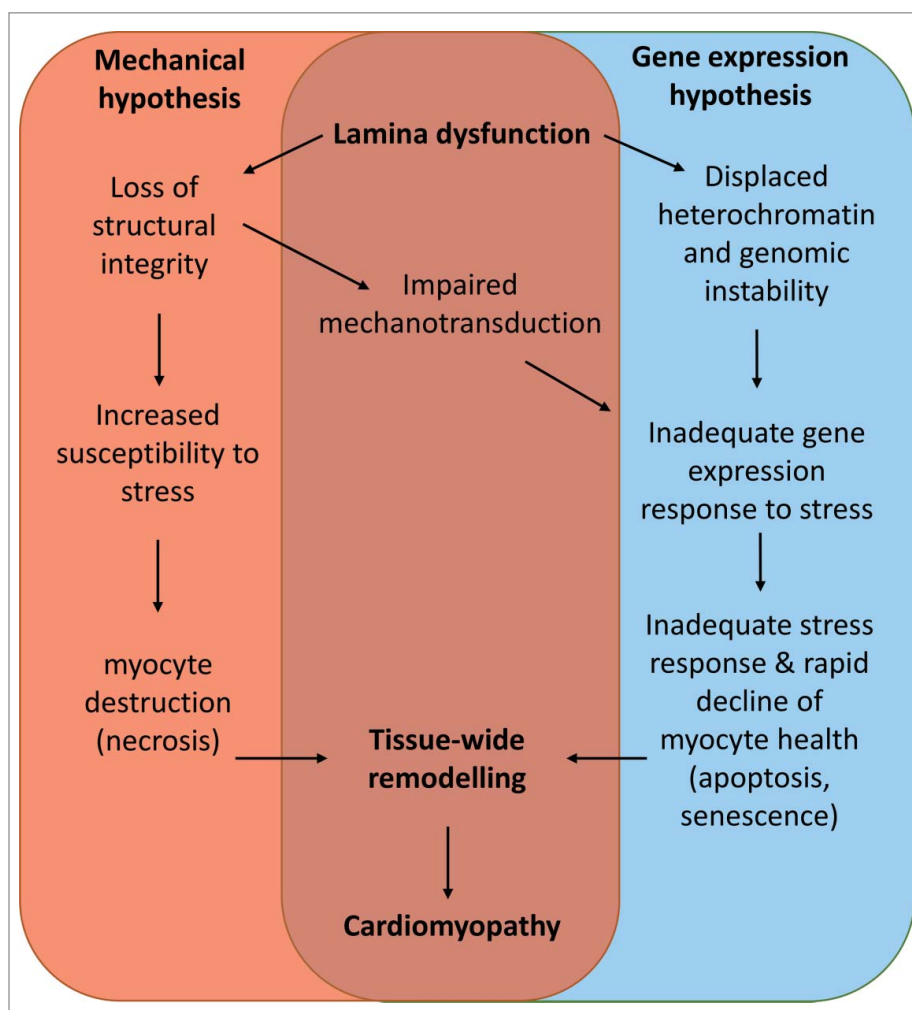


Figure 1. A model unifying the known mechanisms of *LMNA* cardiomyopathy.

encoding phospholamban, which regulates the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) activity. The *PLN* mutation p.Arg14del, that causes DCM with arrhythmia, inhibits SERCA, resulting in a reduction of Ca^{2+} reuptake in diastole.³⁰

The *LMNA* gene is commonly mutated in DCM and accounts for approximately 6–8% of DCM cases in humans.^{7,31} The resultant DCM phenotype is complicated by conduction defects resulting in arrhythmias.³² Genotype-phenotype correlation is poor and the recurrence of common DCM causing mutations in *LMNA* is low; one study reported 165 unique DCM causing mutations to *LMNA*,³³ occurring in all 12 exons of the gene. This diversity makes mechanistic analysis challenging since it is difficult to hypothesize a common mechanism based on specific lamin protein domains and the interactions that might be

disturbed by causal mutations. However, clues to lamin mediated mechanisms may be evident in unique aspects of *LMNA* cardiomyopathy, such as conduction defects.

The cardiac conduction system and conduction defects

Electrical activity in the heart is controlled by specialized ‘pacemaker’ cardiomyocytes residing in the Sino-Atrial node in the atria, which receive signals from the autonomic nervous system. They initiate the propagation of electrical current through the myocardium of the atria causing the cells to contract. At the same time current flows to the Atrio-Ventricular node which initiates the propagation of current down the septum via fibers termed the bundle of His, and Purkinje fibers, which pass current from the apex,

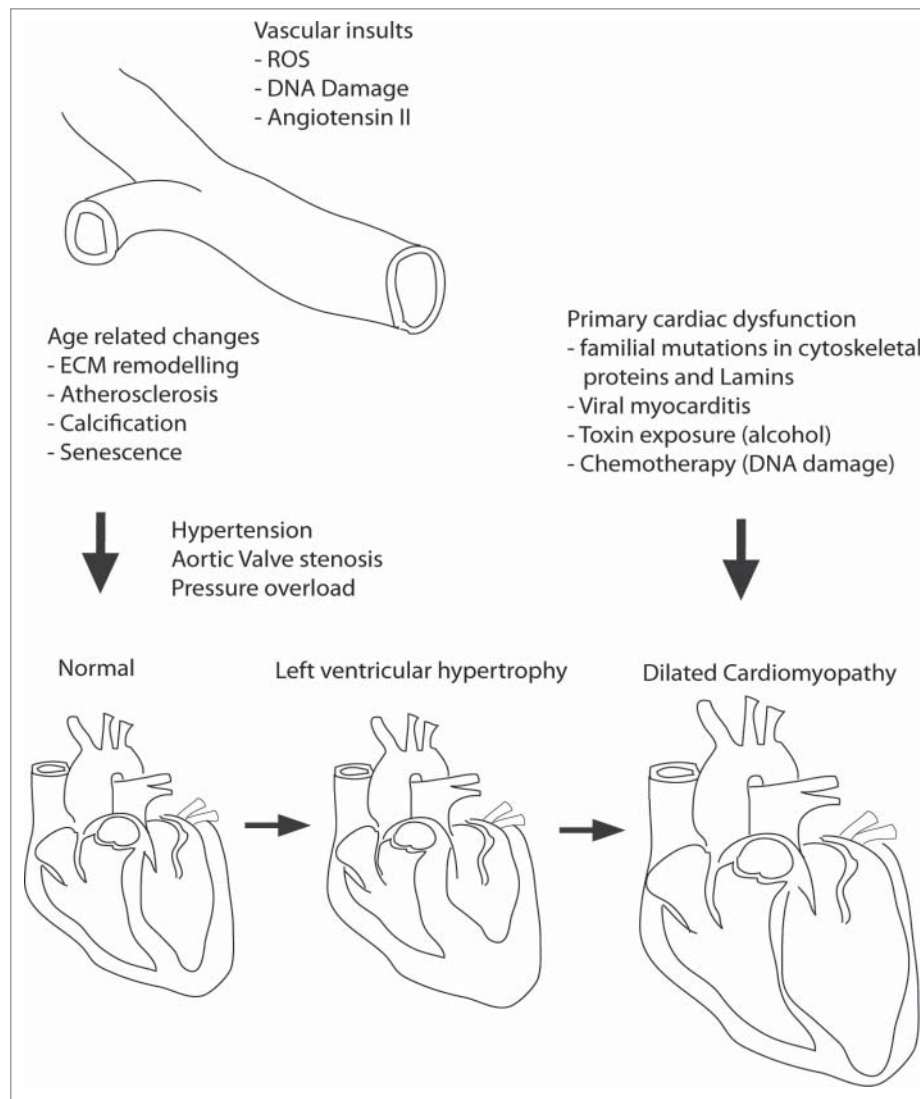


Figure 2. Etiology of Cardiomyopathy onset and progression. DCM is caused in primary and secondary fashion. In secondary it is due to excessive remodelling of the myocardium because of sustained pressure overload caused by vascular remodelling leading to increased overall blood pressure or aortic valve stenosis (hardening). This usually occurs via an intermediate step in which the heart tissue becomes thicker, known as hypertrophy. Primary DCM is caused predominantly by mutations in proteins of the sarcomere, cytoskeleton, or those involved in Ca^{2+} handling. Additionally, viruses and toxins such as alcohol or chemotherapy agents can initiate DCM independent of vascular remodelling. In this context hypertrophy is bypassed.

upwards and side-wards through the ventricular myocardium.³⁴ Cardiomyocytes are excitable cells and have a negative resting membrane potential, allowing current to be propagated cell to cell via gap junctions made up of high conductance channels termed connexins.³⁵ Connexins operate at the polar ends of cardiomyocytes in a junctional complex with the adherens junction (AJ) and desmosome, termed the intercalated disc (ID). Conduction defects could result because of a malfunction at any point during this process.

Notably, almost half of *LMNA* cardiomyopathy patients succumb to sudden cardiac death as a result of a fatal arrhythmia,³⁶ and conduction

defects associated with *LMNA* mutations can substantially precede the onset of DCM symptoms, meaning subtle but fatal arrhythmias may occur before any noticeable change in function. This makes diagnosis difficult in probands who only display cardiac disease.³⁷ Patients displaying muscular dystrophy phenotypes with known *LMNA* mutations can be fitted with cardiac pacemakers/devices as a pre-emptive measure.

Increasingly, patients with *LMNA* mutations also present with nuanced cardiac defects that show features of HCM and ARVC. Therefore, another means of identifying *LMNA* mechanisms may be to look into

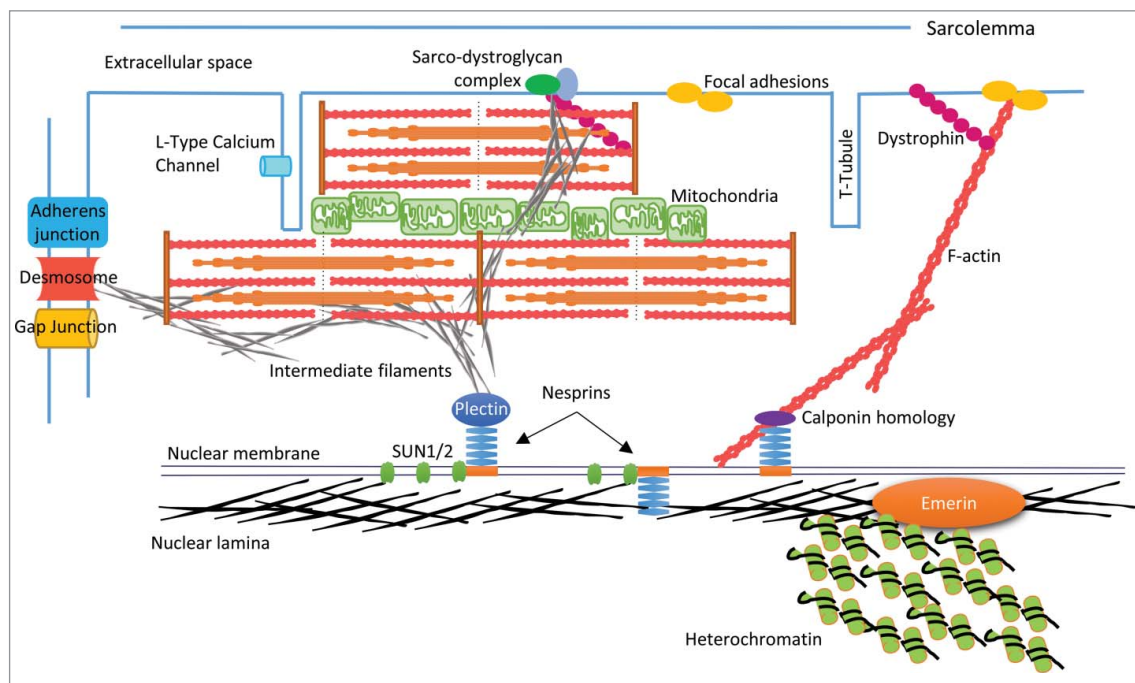


Figure 3. Schematic representation of CM structure. The nuclear lamina associates with LEM proteins i.e., Emerin and heterochromatin on the inner nuclear membrane (INM). Lamins also bind with SUN proteins and nesprins to form the LINC complex, which spans the nuclear envelope (NE), and links to cytoskeletal components (actin, intermediate filaments) via binding domains such as plectin and calponin homology. F-actin extends to the cell periphery and links to membrane anchors such as dystrophin and focal adhesion proteins (e.g. vinculin) thereby creating a mechanical links between the nucleus and ECM. In the context of CMs there may also be interactions with sarcomere structures, which are currently undefined. IFs such as desmin may knit the NE-sarcomere-sarcolemma via the sarco-dystroglycan complex, and provide a mechanical link from the nucleus to the intercalated disc via the cytoskeletal components of the sarcomere and IFs.

the pathways commonly identified in HCM and ARVC which are unique from DCM.

Hypertrophic cardiomyopathy

HCM is an autosomal dominant disease characterized by hypertrophy of ventricular myocardium which is not explained by pressure overload.²⁴ There is associated fibrosis and myocyte disarray as well as high prevalence of arrhythmia and is a common cause of sudden cardiac death in young athletes.³⁸

Like DCM, mechanisms involve mechanical and Ca^{2+} handling changes, although cytoskeletal involvement is less prominent. HCM is usually considered as a disease of the sarcomere. Of 10 genes identified as causal, 9 encode sarcomeric proteins.^{39,40} The 2 most important are *MYBPC3* encoding cardiac myosin-binding protein C (cMyBP-C), and *MYH7* encoding β -MHC, and account for the majority of cases.⁴¹ Mutations mostly lead to substitution of single amino acids, though half of mutations to *MYBPC3* are known to cause truncations to the protein product and lead to haploinsufficiency.^{42,43} Altered myosin

kinetics and increased calcium sensitivity of thin-filaments lead to increased contractility,⁴⁴⁻⁴⁶ and activate hypertrophic signaling pathways. Mutations in troponin T lead to elevated sarcoplasmic reticulum Ca^{2+} content in diastole,⁴⁷ predisposing the myocardium to arrhythmia,⁴⁸ leading to aberrant downstream signaling.⁴⁹

Ca^{2+} handling is disrupted by 2 main mechanisms. Firstly, mutations in cMyBP-C and the troponin complex increases the sensitivity of troponin C to Ca^{2+} .⁵⁰ Troponin is the principal calcium buffer in the SR, therefore, increased affinity should increase calcium levels in diastole.^{51,52} Contractile inefficiency can also compromise the energetics of the cardiomyocyte. Sarcomeric mutations that alter cross-bridge formation kinetics may cause a deficit in ATP availability and could impact upon other ATP requiring processes within the cell, such as Ca^{2+} uptake via SERCA during diastole.⁵³ A myocardial energetics hypothesis is supported by mutations in the $\gamma 2$ subunit of AMP-activated protein kinase, involved in energy sensing, which lead to HCM.⁵⁴

The *LMNA* C591F and *LMNA* R644C mutations lead to phenotypes consistent with HCM.^{14,55} How *LMNA* mutations can influence HCM related mechanisms is not entirely clear. The loss of lamins A/C in isolated cardiomyocytes does not impact Ca²⁺ transients, but the shortening of cardiomyocytes is reduced.⁵⁶ This implies that while the function of SERCA appears to be normal, the activation of myofilaments is hindered and may point to a mechanism involving reduced availability of ATP to the myofilaments.

Arrhythmogenic right ventricular cardiomyopathy

ARVC is characterized by pathological remodelling of the right ventricle, dilatation of cardiac chambers and systolic dysfunction⁵⁷ in which myocyte death, inflammation and fibrofatty replacement of the myocardium are prominent features.⁵⁸ Patients are also prone to arrhythmia and ARVC is known to be another common cause of sudden cardiac death.^{59,60}

Most ARVC mutations occur in desmosomal genes.⁶¹ The desmosome anchors the IFs of one cell to the cytoplasmic membrane of another at the ID in order to create a lattice structure that provides mechanical strength to tissue. Mutations in desmoplakin, plakoglobin, plakophilin-2, and desmoglein-2 all cause ARVC.⁶²⁻⁶⁵ The molecular mechanisms that regulate the progression to ARVC are unclear, but 2 main hypotheses exist. Firstly, desmosomal mutations compromise the integrity of cell-cell interactions and as such make the tissue structure susceptible to mechanical stress, leading to cell detachment and necrosis, causing an inflammatory response. In this setting, fibroadipose deposition is a reparative response to injury. Second is the transdifferentiation model, which proposes that desmosomal perturbations can dysregulate the Wnt/ β -catenin signaling pathway leading to activation of adipogenic and fibrogenic genes and a switch of cell fate from cardiomyocyte to adipocyte.^{66,67}

Recently, patients presenting with ARVC were found to have *LMNA* mutations.^{11,68,69} It remains unclear how NL disruption could be a cause of ARVC, but it is plausible that disruption of the lamina could lead to the destabilisation of cell contacts since the cell membrane and nucleus are linked by a 'molecular daisy chain' of structural proteins. With respect to the transdifferentiation of fibrofatty tissue, emerin, a lamin A binding partner, has a known association with β -catenin and is thought to regulate its nuclear localization.⁷⁰ Hypothetically, *LMNA* mutations which cause ARVC could interfere with the interaction of emerin with β -catenin and cause dysregulation of β -catenin signaling leading to aberrant cell differentiation.

Though phenotypically divergent, the mechanistic processes leading to DCM, HCM and ARVC share important core principles, i.e., structural instability and remodelling of tissue and ECM. *LMNA* mutations are likely to contribute to these processes via disruption of the links between the nucleus and cytoplasm. The mechanisms by which this occurs have been subjected to investigation in a number of animal models.

Modeling *LMNA* cardiomyopathy

In vivo models

Murine models with modified *Lmna* genes have enabled insights into the possible pathological mechanisms driving *LMNA* induced cardiomyopathies and are summarised in Table 2.

Lmna^{H222P/H222P} mice

Global *Lmna*^{H222P/H222P} mice were originally designed to study EDMD, which the human *LMNA* H222P mutation causes. DCM is acquired secondary to EDMD in the human clinic and the *Lmna*^{H222P/H222P} homozygous knockin mice have proven a good model of *LMNA* cardiomyopathy⁷¹ Born without phenotype, they progress to a DCM phenotype at 16 weeks,

Table 2. Clinical *LMNA* mutations and associated mouse model phenotypes

<i>LMNA</i> Mutation	Human Disease	Mouse Model	Disease phenotype	Survival
N195K	DCM-CD	<i>Lmna</i> ^{N195K/N195K}	DCM and Heart failure	12–14 weeks
H222P	EDMD	<i>Lmna</i> ^{H222P/H222P}	DCM and heart failure	Males: 4–9 months Females: 9–13 months
G608G	HGPS	<i>Lmna</i> ^{G609G/G609G}	Progeria - LQT and arrhythmia	3–4 months
M371K	EDMD	MHC- <i>Lmna</i> ^{M371K}	Acute and subacute heart failure	embryonic lethal and 2–7 weeks
Δ K32	L-CMD	<i>Lmna</i> ^{ΔK32/+}	DCM and heart failure	5–6 weeks
L530P	EDMD	<i>Lmna</i> ^{L530P/L530P}	Progeria- with cardiac remodelling	3–7 weeks
E82K	DCM-CD	MHC- <i>Lmna</i> ^{E82K}	DCM	long lived

leading to heart failure and death in males at 5–9 months and females at 7–13 months. They have reduced cardiac function and cardiac fibrosis.⁷¹

In one study, hearts from young pre-phenotypic mice were subjected to gene expression microarray analysis, which identified upregulation of MAPK signaling pathways.⁷² Extracellular signal regulated kinase (ERK1/2), c Jun N-terminal kinase (JNK), as well as p38 branches of MAPK signaling were all upregulated. Subsequent inhibition of JNK and ERK1/2 in mice significantly improved LV functional parameters and led to a reduction in fibrosis.^{73–75} The case for hyperactivation of ERK1/2 was also supported by post-mortem analysis of human heart tissue expressing 2 distinct mutations, *LMNA* ΔK261 and *LMNA* IVS9 + 1 g>a.⁷⁶ Additionally, hyperactivation of the mammalian Target Of Rapamycin (mTOR) signaling pathway inhibited autophagy, a crucial housekeeping process that facilitates the degradation of unwanted proteins and organic components of the cell during severe stress.⁷⁷ Treatment of *Lmna*^{H222P/H222P} mice with temsirolimus, an inhibitor of mTOR, led to activation of autophagy, and amelioration of cardiac decline.⁷⁸ Treatment with angiotensin converting enzyme (ACE) inhibitors also improved myocardial function in these mice. ACE converts inactive angiotensin I to angiotensin II which stimulates sympathetic activation leading to increases in heart rate and vascular tone resulting in pressure overload.⁷⁹ These data imply that by lowering mechanical stress *in vivo*, *LMNA* cardiomyopathy can be delayed or attenuated.

***Lmna*^{N195K/N195K} mice**

The *LMNA* N195K mutation is known to cause DCM with conduction defects in humans.⁸⁰ Accordingly, global *Lmna*^{N195K/N195K} mice developed DCM with associated conduction defects and died at 2–3 months old as a result of arrhythmia.⁸¹ Abnormal desmin localization was observed alongside a reduction in mRNA of *HF1b/Sp4*, a transcription factor that is crucial in the development of the cardiac conduction system, suggesting a possible mechanism for the early presentation of conduction defects in patients. Loss and mislocalisation of connexins 40 and 43, leading to reduced propagation of electrical current through the myocardial tissue, was also observed. These findings point toward a mechanism for conduction defects that may be linked to mechanical susceptibility, as they

implicate lamina dysfunction as a cause for the disruption of cell-cell contacts. The observation that multiple components of the cardiac conduction system are dysregulated in *Lmna*^{N195K/N195K} mice may help to explain why conduction defects are so prevalent in *LMNA* cardiomyopathy.⁸²

***Lmna*^{ΔK32/+} mice**

In man, *LMNA* disease mutations are mostly heterozygous, leading to dominant negative phenotypes. Many model systems of *LMNA* cardiomyopathy in mice show phenotypic changes only when the mutation is homozygous, meaning the contribution of wild-type lamin in disease progression is overlooked. However, global *Lmna*^{ΔK32/+} mice were investigated and found to be pathogenic.⁸³ In humans deletion of lysine at position 32 in the lamin A amino acid sequence causes severe congenital muscular dystrophy (L-CMD) phenotypes.⁸⁴ Mice with this mutation developed DCM that occurred in a 2-step process resulting in death between 35 and 70 weeks. Initially the toxic accumulation of ΔK32-lamin was avoided by proteasomal degradation. However, this resulted in reduced lamin A/C expression, which then initiated the process of cardiac remodelling and DCM. After DCM was established dysfunction of the ubiquitin proteasome system occurred, leading to toxic increases in ΔK32-lamin. These mice also showed earlier onset DCM as a result of exercise-induced stress.⁸⁵

Other models of *LMNA* mutations

In man, the *LMNA* M371K mutation causes EDMD.⁸⁶ In MHC-*Lmna*^{M371K} mice, cardiac specific overexpression of *LMNA* M371K led to mice with very low survival at birth. Mice that survived died between 2–7 weeks from cardiac defects.⁸⁷ This study suggests that accumulation of mutant M371K lamin A is toxic in the presence of endogenous wildtype lamins in a cardiomyocyte specific setting. Importantly, this study also investigated overexpression of wildtype lamin A/C in the heart. These mice displayed no phenotypic defects and were long lived, supporting the idea that mutant *LMNA* is a toxic driver of disease phenotypes, perhaps operating by disrupting lamin structure and function, by dysregulation of lamin processing and binding, or even by disrupting the balance of lamin isoform expression.

The DCM causing mutation, *LMNA* E82K, has also been investigated *in vivo* in a cardiac specific manner. *MHC-Lmna*^{E82K} mice showed evidence of cardiac dysfunction at 6 months of age indicated by a reduction in cardiac function and myocardial remodelling.⁸⁸ Fas and mitochondrial pathways of apoptosis were identified as the mechanisms responsible for cardiac decline in this model.

In the clinic, the *LMNA* L530P mutation leads to EDMD. *In vivo* global *Lmna*^{L530P/L530P} mice had a progeria phenotype and also showed a cardiac phenotype, described as displaying features consistent with pulmonary hypertension. They had enlarged hearts and fibrosis, suggesting a program of pathological cardiac remodelling was induced.⁸⁹ Moreover, when modeled in *C. elegans* the corresponding mutation *Lmn-1* L535P caused a muscular dystrophy characterized by increased resistance of muscle nuclei to mechanical strain alongside structural disorganisation of muscle actin filaments.⁹⁰

Lmna knockout models

Though not clinically relevant, global *Lmna*^{-/-} mice die between 6–8 weeks of age because of DCM and heart failure⁵⁶ and share mechanistic traits with *Lmna*^{H222P/H222P} mice including impaired autophagy.⁹¹ Intervention with the mTOR inhibitor rapamycin significantly improves cardiac function and survival in *Lmna*^{-/-} mice, and strengthens the argument for aberrant mTOR activation in *LMNA* cardiomyopathy.

Further investigation showed that *Lmna*^{-/-} cardiomyocytes were structurally compromised. This occurs via the disruption of nesprin1 α resulting in uncoupling of the nucleus from the cytoskeleton leading to mechanical instability and defective transmission of force.⁹² In support of this finding, desmin was also mislocalised.⁵⁶ Activation of hypertrophic genes was attenuated, suggesting that *Lmna*^{-/-} mice were unable to adapt to DCM progression with compensatory hypertrophy, accounting for rapid disease progression. Connexins were also mislocalised contributing to attenuated contractility and also arrhythmia.^{93,94}

Lmna haploinsufficiency was also investigated. *Lmna*^{+/-} mice displayed early onset cardiac conduction system disease and late onset DCM,⁹⁵ which could be alleviated by exercise and β -blockers.⁹⁶ Application of pathological hemodynamic stress led to

a blunted hypertrophic response due to impaired activation of the mechanosensitive gene, *Egr1*,⁹⁷ and provided evidence that mechanotransduction signaling pathways and pathophysiological adaptations to stress can be inhibited by lamina disruption.

In vivo models have been invaluable in the observation of critical molecular events, which underpin the pathology of *LMNA* cardiomyopathy, especially with regard to conduction defects. However, a complete understanding of mechanisms will likely require rigorous investigation of early, pre-phenotypic timepoints to identify the earliest possible molecular changes immediately downstream of lamin dysfunction.

In vitro models

Analysis of *LMNA* cardiomyopathy mutants in single cell models have also provided important mechanistic insights into disease mechanisms at the molecular level.

Evidence for the mechanical hypothesis

Studies performed in fibroblasts showed that the DCM causing *LMNA* mutations M371K, Δ K32 and N195K failed to restore nuclear stiffness after deformation, and the mutant lamin proteins were more soluble than wild type lamin A. Moreover, Δ K32 and N195K mutant lamin proteins failed to assemble into filaments *in vitro*, instead forming aggregates, and mimicked the loss of lamin function.⁹⁸

Structural analysis of DCM mutations E161K and R190W showed alterations in secondary and tertiary structures leading to perturbed intrinsic self-assembly of high order lamin structures.⁹⁹ At the level of electron microscopy, the lamin lattice networks showed substantial organisational changes and reduced elasticity. Another *LMNA* DCM mutation S143P, common in Finnish patients, was also found to undergo reduction in self-assembly behavior *in vitro* and was associated with an elevated unfolded protein response according to whole genome analysis.¹⁰⁰

An hypothesis has been put forward to explain the impact of these findings. In fully differentiated mechanical structures such as striated muscle, lamins A and C are highly expressed. It is thought that their flexible rheological (gel-like) behavior, acts as a 'valve' for the B-type lamins which, in contrast, resist deformation.¹⁰¹ Therefore, if a proportion of the A-type lamins are mutant, and the ability of the nucleus to soften in

response to strain is reduced, then the lamina network is likely to collapse in response to a relatively low mechanical stress threshold. Accordingly, a number of myopathic *LMNA* mutations have been tested in an *in situ* model of *D. melanogaster* body wall muscle, and an *in vitro* model of mouse embryonic fibroblasts, which found increases in nuclear strain and decreases in nuclear displacements in response to mechanical stretch.⁹⁸

Evidence for the gene expression hypothesis

A number of studies have investigated the role of lamin dysfunction on mechanotransduction pathways—signaling mediated by physical interactions—by examining gene expression responses. Investigation of *Lmna*^{-/-} mouse fibroblasts found impaired activation of mechanosensitive genes *Iex1* and *Egr1* in single cell models of mechanical stretch.^{102,103} It has also been shown that the NL may be able to detect perturbations in force and convert these into adaptive or pathological gene expression responses. For example, disruption of the NL by *Lmna* deficiency attenuated NF-κB mediated transcriptional response to mechanical or cytokine stimulation despite increased transcription factor binding, implying that lamins are crucial for transcriptional activation.¹⁰⁴⁻¹⁰⁶

In vitro studies have also provided detailed insight on the impact of *LMNA* disruption on the mechanical properties of cells and have identified that these can elicit abnormal gene expression and signaling responses. However, despite the wealth of investigations into *LMNA* cardiomyopathy mutations in isolated models, analyses have rarely been undertaken in isolated cardiomyocytes; thus the cardiomyocyte specific effects of these mutations are largely undefined. One study has addressed this by investigating induced pluripotent stem cell derived cardiomyocytes from a patient harbouring the *LMNA* R225X mutation and found that when cardiomyocyte contraction was initiated by electrical stimulation, the cells underwent apoptosis.¹⁰⁷

In summary, data from the clinic and model systems suggests that structural defects drive the onset of disease by contributing to defective electrical signaling, and also by inhibiting efficient molecular signaling responses to mechanical stress. In addition, a common theme in models investigating *LMNA* cardiomyopathy is the activation of cellular stress

responses—apoptosis, autophagy and the unfolded protein response—indicating that certain lamin mutants may be toxic to cells, a feature which has until now been understudied.

Lamin toxicity in cardiomyopathy

One model yet to be tested in the context of *LMNA* cardiomyopathy is the prelamin A toxicity model. Prelamin A toxicity is central to a number of laminopathy sub-types, primarily the premature aging disorders. In HGPS, for example, the final enzymatic cleavage of prelamin A, performed by *ZMPSTE24*, is abolished and the protein remains permanently farnesylated, meaning it cannot be inserted efficiently or completely into the NL.¹⁰⁸ In the most common form of HGPS, this occurs because of a mutation that leads to the deletion of 50 amino acids which contain the *ZMPSTE24* cleavage site,¹⁰⁹⁻¹¹¹ resulting in a truncated prelamin A mutant protein called progerin. Loss of function mutations to *ZMPSTE24* lead to prelamin A accumulation and can also drive HGPS phenotypes.¹¹² Prelamin A accumulation is also an important mediator in normal aging in a number of tissues, including the vasculature.¹¹³ It is not known, however, whether this is relevant in myocardial aging.

Progerin and prelamin A are thought to drive disease phenotypes by disrupting nuclear morphology and heterochromatin distribution as well as DNA damage repair pathways resulting in premature senescence.¹¹⁴⁻¹¹⁶ Heterochromatin instability appears to be partly responsible for the defective recruitment of repair factors to sites of DNA damage.^{117,118} In addition, prelamin A accumulation causes nuclear pore complex dysfunction which also impairs recruitment of DNA repair proteins.¹¹⁹ Interestingly, one study investigated the *LMNA* L306R mutation, which caused a premature aging syndrome with severe ARVC presentation; cells with this mutation had dysmorphic nuclei, elevated levels of DNA damage and underwent premature cellular senescence.¹¹ Moreover, stem cell derived cardiomyocytes with the *LMNA* R225X mutation displayed nuclear morphology defects and premature senescence under stress.¹⁰⁷ These studies provide the clearest evidence yet that premature aging mechanisms may be partly responsible for *LMNA* cardiomyopathy phenotypes.

There is evidence to suggest that prelamin A/progerin accumulation is important in the establishment

of cardiac disease phenotypes. For example, HGPS patients were observed to suffer cardiomegaly and cardiac dilatation toward the end of life¹²⁰ and HGPS patients who survived to older ages displayed cardiac remodeling and atrial enlargement.¹²¹ A mouse model of HGPS has also shown evidence of cardiac dysfunction.¹²² Recently, a mutation in *ZMPSTE24* was identified that caused a substantial reduction in *ZMPSTE24* activity and led to DCM associated with metabolic syndrome.¹⁶ Meanwhile, *Zmpste24*^{-/-} mice showed evidence of myocardial disruption at 3 months of age.¹²³ The *LMNA* p.T655fsX49 mutation caused accumulation of non-farnesylated prelamin A, leading to cardiac conduction defects in humans.¹³ Accordingly, accumulation of non-farnesylated prelamin A led to late onset DCM in mice expressing a homozygous 'non-farnesylated prelamin A only' allele.¹²⁴ DCM mutations have also been shown to accumulate prelamin A in model systems, as expression of the *LMNA* R89L mutant caused accumulation of prelamin A *in vitro*.¹²⁵ Moreover, some of the murine *LMNA* cardiomyopathy models have shown nuclear morphology defects and heterochromatin disorganisation, both hallmarks of prelamin A/progerin toxicity. Further investigation is now required to determine how prevalent the accumulation of lamin A precursors is in cardiomyopathy patient hearts.

Therapeutic potential

Modulation of mTOR signaling currently provides the most promising way forward for the treatment of *LMNA* cardiomyopathy specifically.^{126,127} For laminopathies as a whole, exon skipping¹²⁸ and influencing the splicing of *LMNA* toward lamin C to avoid the dominant negative effects of lamin A mutants,¹²⁹ are being investigated as potential therapies and may have relevance to *LMNA* cardiomyopathies. In prelamin A accumulating diseases such as HGPS, farnesyl transferase inhibitors (FTIs) have been through clinical trials with modest success.¹³⁰ This was followed up by trials of a combination therapy of FTIs with statins and bisphosphonates, which inhibit upstream processing in the Acetyl-CoA pathway of cholesterol synthesis and protein prenylation (which includes farnesylation), but again showed limited benefit.¹³¹ Inhibition of prelamin A processing enzymes such as ICMT, which controls carboxymethylation of prelamin A, may instead be beneficial in the context of prelamin A toxicity, via

regulation of mTOR.¹³² Moreover, Remodelin, a small molecule inhibitor of N-acetyltransferase 10 (NAT10), alleviates many cellular abnormalities in HGPS, potentially operating via a novel mechanism involving microtubule reorganisation, and shows much promise at the pre-clinical stage.¹³³

Future directions

The gene expression and mechanical hypotheses have been well investigated in *LMNA* cardiomyopathy, and important cell signaling pathways have been established. However, questions regarding the role of Ca²⁺ signaling and myocardial energetics remain unanswered. Moreover, the pleiotropic effects of single *LMNA* mutations, such as the R644C mutation involved in EDMD, DCM, HCM and ARVC progression,¹³⁴ suggest that external factors may be important in the establishment of disease. The nature of these stimuli may impact the direction of disease progression, implying that the study of epigenetics and intercellular communication, for example, may also be important in *LMNA* cardiomyopathy.

The toxicity of prelamin A or other lamin variants is also potentially important and requires further investigation. Associated pathways involving DNA damage and premature senescence should also be considered both in the context of cardiomyopathies and normal myocardial aging. Therapies for laminopathies driven by accumulation of unprocessed prelamin A or truncated lamin mutants are currently under investigation with some having been to clinical trials. If *LMNA* cardiomyopathy is driven by toxic accumulation of lamin variants, these therapies may also be important in the future treatment of some *LMNA* cardiomyopathies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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