The structural and gene expression hypotheses in laminopathic diseases—not so different after all

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ABSTRACT **Laminopathies are a diverse group of rare diseases with various pathologies in different tissues, which are linked to mutations in the *LMNA* gene. Historically, the structural disease model proposed mechanical defects of the lamina and nuclear fragility, the gene expression model impairment of spatial chromatin organization and signaling pathways as underlying mechanisms leading to the pathologies. Exciting findings in the past few years showing that mechanical forces are directly transmitted into the nucleus, where they affect chromatin organization and mechanoresponsive signaling molecules, have led to a revised concept of an integrative unified disease model, in which lamin-mediated pathways in mechanotransduction and chromatin regulation are highly interconnected and mutually dependent. In this Perspective we highlight breakthrough findings providing new insight into lamin-linked mechanisms of mechanotransduction and chromatin regulation and discuss how a combined and interrelated impairment of these functions by *LMNA* mutations may impair the complex mechanosignaling network and cause tissue-specific pathologies in laminopathies.**

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THE HISTORY OF LAMINOPATHIES

Since the discovery of the first disease-linked mutation in the *LMNA* gene in 1999 (Bonne *et al.*, 1999), which was associated with Emery–Dreifuss muscular dystrophy (EDMD), the complexity of clinical pathologies of lamin-linked diseases, now called laminopathies, has steadily increased. Today, more than 400 different *LMNA* mutations are known (www.umd.be/LMNA/), which give rise to more than 15 different diseases, affecting a wide range of tissues (Ho and Hegele, 2019). Based on the predominantly affected tissues, laminopathies are grouped into four major types: diseases affecting 1) striated and cardiac muscle, such as EDMD and dilated cardiomyopathy (Brull *et al.*, 2018), 2) peripheral nerves, such as Charcot–Marie–Tooth disorder type 2B1 (Ho and Hegele, 2019), 3) adipose and bone tissue, such as familial partial lipodystrophy of Dunnigan type 2 (FPLD2) (Vigouroux *et al.*, 2018), and 4) multisystemic disorders including a wide range of premature aging syndromes such as Hutchinson–Gilford progeria syndrome (HGPS), mandibuloacral dysplasia, and an atypical Werner syndrome (Vidak and Foisner, 2016). *LMNA* is among the genes in the human genome with the largest numbers of reported mutations. Most laminopathies are caused by dominant missense mutations located throughout *LMNA* (Ho and Hegele, 2019), with the prominent exception of HGPS, which is predominantly caused by a silent mutation in exon 11 that affects splicing of *LMNA* pre-mRNA and posttranslational modification of prelamin A protein (Vidak and Foisner, 2016).

Lamins are nuclear intermediate filament proteins that form a filamentous meshlike structure beneath the inner nuclear membrane called nuclear lamina (Turgay *et al.*, 2017). Four major lamin types have been identified in mammalian cells: lamin A and a smaller splice variant, lamin C, encoded by *LMNA,* and lamin B1 and B2, encoded by *LMNB1* and *LMNB2*, respectively (Gruenbaum and Foisner, 2015). B-type lamins are universally expressed, while A-type lamins are expressed later during development and in most differentiated cell types. Lamin A, B1, and B2 are initially expressed as prelamins and are posttranslationally processed in three key steps: 1) farnesylation of the cysteine in the C-terminal -CaaX

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Abbreviations used: EDMD, Emery–Dreifuss muscular dystrophy; ERK, extracellular regulated kinase; FPLD2, familial partial lipodystrophy of Dunningan type 2; GFP, green fluorescent protein; HGPS, Hutchinson–Gilford progeria syndrome; LADs, lamina-associated domains; LINC, linker of nucleoskeleton and cytoskeleton; MKL1, megakaryoblastic leukemia 1; MRTF-A, myocardin-related transcription factor A; PRC2, polycomb repressor complex 2; SREBP1, serum response element binding protein 1; TGFβ, tranforming growth factor beta; YAP, Yes-associated protein; ZMPSTE24, zinc metallopeptidase STE24.

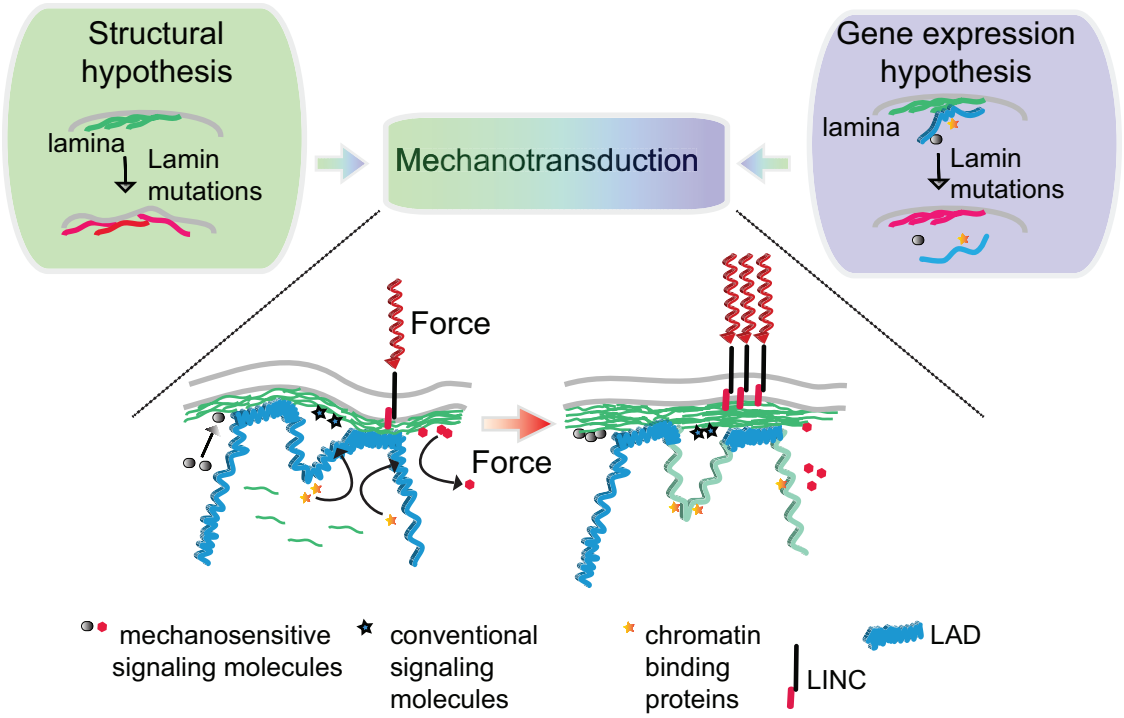

FIGURE 1: Mechanotransduction pathways bridge the structural and gene expression disease hypotheses of laminopathies. (Top) The structural hypothesis suggests *LMNA* mutation–linked structural defects of the lamina leading to mechanical fragility of the nucleus; the gene expression hypothesis proposes changes in spatial organization of chromatin and signaling molecules. (Bottom) Summary of mechanotransduction pathways potentially deregulated in laminopathies. Mechanical forces are transmitted into the nucleus through the LINC complex and the lamina. Increased forces reinforce these mechanoresponsive structures, leading to partial unfolding of proteins and stretching of chromatin, which in turn creates (gray globes) or removes (red globes) binding sites for mechanosensitive signaling molecules in lamina molecules and increases the accessibility of decompacted chromatin for chromatin-binding proteins. In contrast, "conventional" signaling molecules are nonresponsive to these mechanical changes.

sequence, 2) proteolytic cleavage of the -aaX tripeptide, and 3) carboxymethylation of the C-terminal cysteine. While B-type lamins maintain the hydrophobic farnesyl- and carboxymethyl groups and are tightly linked to the inner nuclear membrane, lamin A is further processed by ZMPSTE24-mediated proteolytic cleavage of the C-terminal 15 residues including the farnesyl and carboxymethyl groups (Gruenbaum and Foisner, 2015). As a consequence, mature lamin A lacks the hydrophobic groups and can also be found in the nuclear interior, where it fulfills important functions in chromatin organization and stem cell regulation (Naetar *et al.*, 2017). The HGPS-linked lamin A variant lacks the ZMPSTE24 cleavage site and accumulates at the inner nuclear membrane (Vidak *et al.*, 2015).

In parallel to the identification of an increasing number of *LMNA*-linked diseases, tremendous progress has been made in our understanding of the diverse disease mechanisms in different laminopathies. Historically, two models, the structural and gene expression models, were proposed to answer the puzzling question of how mutations in only one gene can cause such a variety of clinical phenotypes. Over the past two decades novel, sometimes surprising functions of lamins have been revealed in both areas, and more recently, it became clear that these models are highly interconnected and interrelated, more and more obliterating a clear distinction between them. Below, we briefly highlight the main breakthrough discoveries in mechanical and gene regulatory functions of lamins and discuss molecular pathways by which these may work together to generate the cellular and organismal phenotypes and pathologies in laminopathies.

THE STRUCTURAL MODEL

According to the structural hypothesis, lamin mutations lead to structural alterations of the lamina, causing increased nuclear fragility and mechanosensitivity (Figure 1). This could explain the effect of *LMNA* mutations in mechanical load-bearing tissues such as striated muscle, bone, cartilage, and cardiovascular tissue, in particular. Biophysical studies brought exciting new insight into the different mechanical properties of lamins, suggesting that A-type lamins are viscoelastic, providing nuclear stiffness, while the elastic B-type lamins allow deformability (Swift *et al.*, 2013). Furthermore, lamin A expression levels seem to scale with the stiffness of the cellular environment, and changing the cellular environment affects lamin A levels and vice versa (Buxboim *et al.*, 2014). These findings increasingly pointed toward a role of lamins in mechanotransduction, a process of direct force transmission from the cellular environment via adherens junctions and the cytoskeleton into the nucleus, where the mechanical forces are translated into biochemical signals (Osmanagic-Myers *et al.*, 2015). Mechanotransduction requires lamins and several proteins of the nuclear envelope, such as the inner nuclear membrane protein emerin, and SUN and nesprins, proteins of the linker of nucleoskeleton and cytoskeleton (LINC) complex that forms a physical connection between the cytoskeleton and the lamina (Ho *et al.*, 2013; Guilluy *et al.*, 2014).

In support of mechanotransduction playing a role in laminopathies, nuclei in striated muscle diseases and in HGPS showed altered biomechanical properties and impaired mechanotransduction

(Dahl *et al.*, 2006; Zwerger *et al.*, 2013; Bertrand *et al.*, 2014; Laurini *et al.*, 2018; Osmanagic-Myers *et al.*, 2019). Reducing SUN1 protein or disrupting the LINC complex in laminopathic mouse models corrected nuclear defects and enhanced longevity (Chen *et al.*, 2012; Kim *et al.*, 2018), suggesting that impaired mechanotransduction contributes to laminopathic pathologies. Nevertheless, as outlined below, it became increasingly clear that the mechanical disease hypothesis alone cannot explain the level of diversity in laminopathic pathologies.

THE GENE EXPRESSION MODEL

The gene expression model is based on findings that lamins regulate gene expression at multiple levels. First, the lamina, which includes lamins and a multitude of ubiquitous and tissue-specific proteins of the inner nuclear membrane (Worman and Schirmer, 2015), affects various signaling pathways either by sequestering transcription factors or signaling molecules to the periphery, away from their intranuclear targets, or by providing scaffolds for efficient activation of signaling molecules (Gerace and Tapia, 2018; Figure 1). Many disease-linked lamin mutations interfere with this function of the lamina, either directly through weakening or strengthening interactions of lamins with signaling molecules or indirectly, by affecting signaling-regulating lamin-binding proteins (Brull *et al.*, 2018; Serebryannyy and Misteli, 2018). A prominent example is serum response element binding protein 1 (SREBP1), a transcription factor important for adipogenic differentiation and energy metabolism, whose interaction with lamin A and thus activity are affected in FPLD2 (Vadrot *et al.*, 2015). Another example is extracellular regulated kinase (ERK 1/2) sequestration and hyperphosphorylation in cardiomyopathy caused by the H222P lamin mutant (Chatzifrangkeskou *et al.*, 2016).

Second, the lamina plays an important role in spatial chromatin organization and gene silencing by tethering long heterochromatic genomic regions, so-called lamina-associated domains (LADs), to the nuclear periphery (Gruenbaum and Foisner, 2015; van Steensel and Belmont, 2017). Lamins A/C also regulate chromatin in the nuclear interior, affecting epigenetic pathways and differentiation-specific gene expression (Lund *et al.*, 2013, 2015; Gesson *et al.*, 2016). In line with impaired lamin-mediated chromatin regulation in laminopathies, chromatin organization is affected in HGPS (McCord *et al.*, 2013), muscle laminopathies (Perovanovic *et al.*, 2016; Marreddy Cheedipudi *et al.*, 2019), and FPLD2 (Oldenburg *et al.*, 2017; Paulsen *et al.*, 2017; Briand *et al.*, 2018).

Third, lamins also directly regulate epigenetic modifier complexes, such as polycomb repressor complex 2 (PRC2), which sets the repressive H3K27me3 histone mark (Cesarini *et al.*, 2015), and NURD nucleosomal remodeling complex (Pegoraro *et al.*, 2009). Evidence is accumulating that these factors are impaired in laminopathies, such as lipodystrophies and HGPS (Pegoraro *et al.*, 2009; Briand *et al.*, 2018).

PATHWAYS LINKING THE STRUCTURAL AND GENE EXPRESSION MODELS

Emerging data on the role of lamins in mechanotransduction (Ho *et al.*, 2013; Guilluy *et al.*, 2014; Schwartz *et al.*, 2017), including exciting new findings in HGPS models (Kim *et al.*, 2018; Osmanagic-Myers *et al.*, 2019), suggest that a clear distinction between structural and gene expression disease models in laminopathies is no longer justified, as both lamin-mediated activities seem to be tightly connected and interdependent. Mechanotransduction seems to be the key player connecting the two models (Figure 1). This concept proposes that physical forces are transmitted through integrins, the cytoskeleton, the LINC complex, and lamins to the nucleus, where the mechanical signal is translated into biochemical and genetic outputs. The mechanistic basis of force translation may involve force-induced structural unfolding of proteins that creates or removes binding sites for mechanosensitive proteins (Figure 1). Any structural changes in the components of this mechanoresponsive machinery, including the lamins, are expected to result in defective mechanoresponse and altered gene expression (Osmanagic-Myers *et al.*, 2015). One challenge in future research on laminopathies will be to unravel at molecular detail how these unified mechanosignaling pathways contribute to the cellular and organismal pathologies in laminopathies. Based on recent emerging data, several possibilities can be envisaged for how this may be accomplished mechanistically:

Force may directly affect spatial chromatin organization and structure. Using a green fluorescent protein (GFP)-tagged reporter gene, Tajik and colleagues showed that application of force through RGD-magnetic beads induced chromatin stretching, initiating transgene expression, presumably through chromatin decompaction (Tajik *et al.*, 2016). Whether a similar mechanism works for endogenous genes and how specificity can be generated are still open questions, but it is tempting to speculate that force-mediated changes in chromatin accessibility may lead to a context-dependent response in cell differentiation, dependent on the availability of cell type specific transcription factors. Mechanical forces, generated for example by changes in cell geometry or extracellular matrix composition, also affect spatial chromatin organization and gene expression (Wang *et al.*, 2017). The detachment of tissue-specific facultative LADs or specific genes from the nuclear envelope is usually linked to gene activation. However, whether gene detachment may also be linked to gene stretching, as hypothesized in the "tug-of-war" mechanism (van Steensel and Belmont, 2017), remains to be seen. In this scenario, movement of genes in inter-LAD regions to the nuclear interior and maintained attachment of neighboring LADs at the nuclear periphery may directly pull on inter-LAD regions and affect chromatin compaction (Figure 1). Furthermore, attachment of LADs to the nuclear periphery has recently been shown to decrease chromatin compaction in the nuclear interior (Ulianov *et al.*, 2019). Although lamins are clearly key factors in force transmission and spatial chromatin organization, it is uncertain whether these putative "mechanosensitive" movements of genes and genomic regions are affected by lamin A mutants. In support of this hypothesis, expression of a EDMD-linked lamin mutant in *Caenorhabditis elegans* affected differentiation of mechanical load-bearing muscle cells by impairing movement of a muscle but not gut promoter–driven transgene to the cell interior (Mattout *et al.*, 2011).

An elegant study by Le and coworkers (2016) provided mechanistic insight into how mechanical forces can affect cell lineage commitment through force-induced spatial chromatin rearrangements linked to epigenetic and gene expression changes. Application of force to epidermal stem cells caused translocation of emerin to the outer nuclear membrane and local actin filament assembly, which in turn led to detachment of chromatin from the nuclear periphery and loss of the repressive H3K9me3 histone marks. Concomitant depletion of G-actin led to reduction of Pol II activity, accompanied by a general increase in PRC2-mediated repressive H3K27me3 marks and reduced gene expression.

There is evidence not only that external mechanical forces transmitted into the nucleus can directly affect gene expression through lamin-mediated pathways, but also that, vice versa, lamin-mediated changes in signaling pathways can affect extracellular matrix protein expression in part through activation of transforming growth factor

beta (TGFβ) and wnt/ß-catenin pathways (Hernandez *et al.*, 2010; Vidak *et al.*, 2015; Chatzifrangkeskou *et al.*, 2016; Le Dour *et al.*, 2017a,b; Bernasconi *et al.*, 2018), which in turn alters the mechanical properties of the cell environment.

An alternative, indirect mechanism for translating mechanical forces into gene expression changes is the activation of mechanoresponsive transcription factors sensitive to F/G-actin levels, such as yes-associated protein (YAP) and megakaryoblastic leukemia 1 (MKL1), also known as myocardin-related transcription factor (MRTF-A), both of which have been shown to be affected in muscle laminopathies (Ho *et al.*, 2013; Bertrand *et al.*, 2014) and HGPS (Osmanagic-Myers *et al.*, 2019).

In summary, we propose to consider a revised integrative laminopathy disease model suggesting that the impairment of tightly linked and interrelated lamin-mediated pathways in mechanotransduction, chromatin organization, and gene expression jointly contribute to the cellular and organismal phenotypes and pathologies. This is particularly evident for the observed impairment of stem cell function and the fibrotic phenotype, which are affected by both mechanical cues and "classical" signaling pathways. Fibrosis is linked to up-regulation of TGFß/CTGF signaling in muscle laminopathies (Chatzifrangkeskou *et al.*, 2016; Bernasconi *et al.*, 2018) and to impaired mechanoresponse in HGPS cardiovascular tissue (Osmanagic-Myers *et al.*, 2019). Similarly, diverse signaling pathways and mechanical cues are major regulators of stem cell differentiation (Miroshnikova *et al.*, 2017). We are convinced that future research on laminopathies will reveal many more examples of a combined mechanosignaling/gene expression impairment in laminopathic pathologies at the mechanistic level.

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