



INSIDE LOOK

Cell biology and mechanopathology of laminopathic cardiomyopathies

Yekaterina A. Miroshnikova^{1,2,3*}, Tim Hammesfahr^{3*} , and Sara A. Wickström^{1,2,3} 

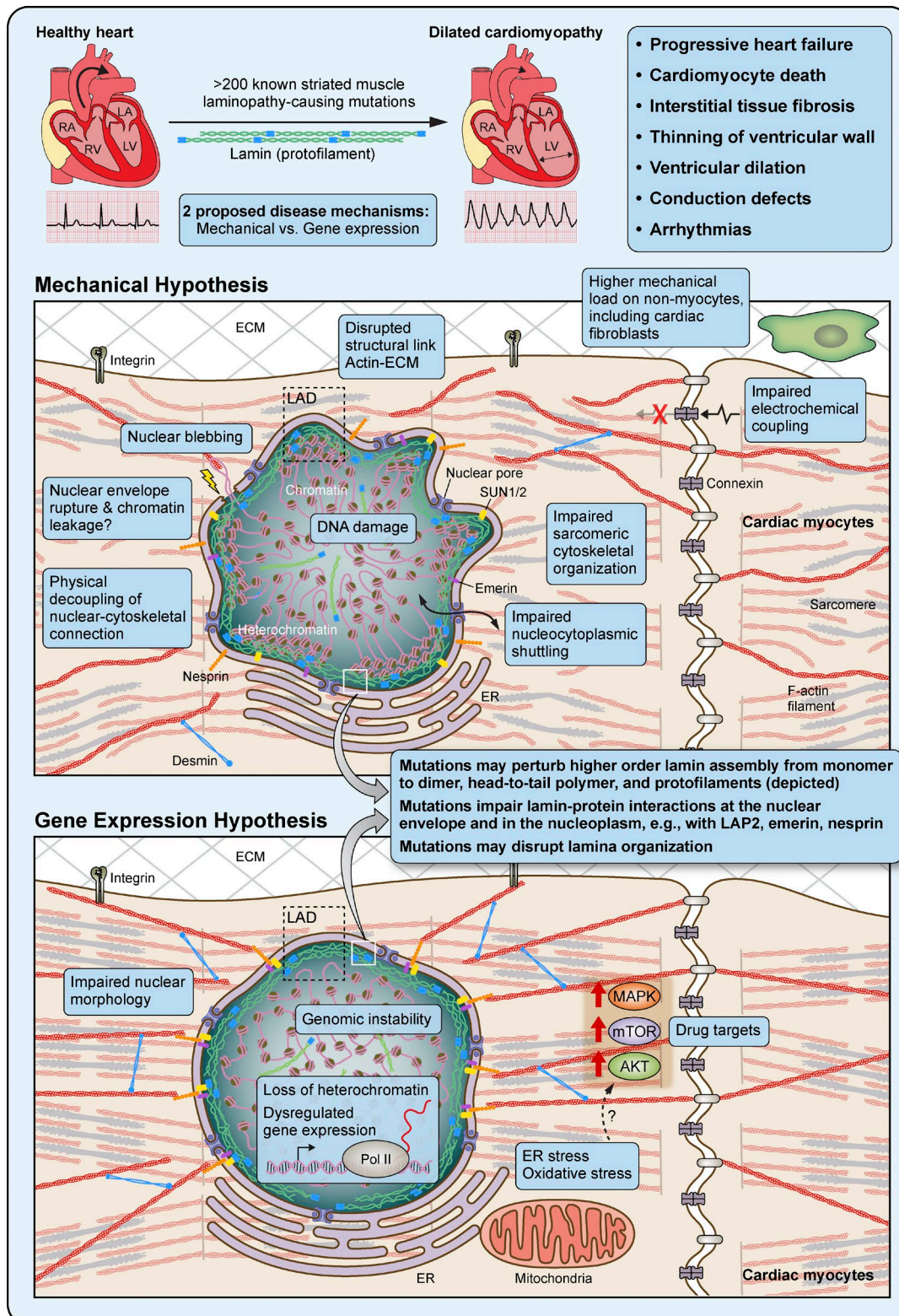


Illustration by Patrick Lane (patrick@sceyencestudios.com).

The mammalian genome encodes A-type lamins A and C (*LMNA* splice variants) expressed only in differentiated cells, and the ubiquitously expressed B-type lamins (1). Attributed to nearly half of the >600 described pathogenic *LMNA* mutations, striated muscle laminopathies are the most prevalent type of laminopathy. Life-limiting cardiac dysfunction is the unifying feature of these diseases that are caused by altered biophysical properties of muscle cells, resulting in thinning of ventricular walls, enlargement of ventricular volume, and impaired electrophysiological conduction. These defects compromise cardiac output and trigger malignant arrhythmias (2).

Lamins are the key component of the nuclear lamina separating the inner nuclear membrane from chromatin. Laminopathy-causing mutations are scattered along the *LMNA* gene. They may perturb lamin assembly to filaments and protofilaments or disrupt binding partner interactions, compromising lamin function and distribution. How exactly the various mutations in the *LMNA* gene disrupt the nuclear lamina and associated cellular functions to elicit the extremely heterogeneous pathological phenotypes with strikingly poor genotype-to-phenotype correlation remains a challenging open question. Two cardiomyopathy-driving mechanisms have been proposed: the mechanical and the gene expression models (2).

Despite expression in most differentiated cells, *LMNA* mutations have the most detrimental effects on the heart, a mechanically challenged tissue. In the mechanical model, loss of nuclear integrity impairs the ability of cells to cope with mechanical stress, leading to myocyte death, increased mechanical load on non-myocytes, and pathological heart remodeling. Additionally, the absence of lamin-mediated nuclear-cytoskeletal links abrogates mechanotransduction (3).

The gene expression model builds on lamins' interactions with specific genomic loci, regulating their structure, epigenetic state, and transcriptional activity. Lamins interact with heterochromatin at regions termed lamina-associated domains (LADs) as well as in the nuclear interior, and impaired interactions alter chromatin

architecture and positioning to disrupt gene regulation (4). Lamins have also been shown to modulate nuclear traffic, to interact with and regulate transcription factors and signaling molecules, and to regulate redox stress (5, 6).

Despite the separation of the two models, it is becoming clear that nuclear mechanotransduction is intimately linked to chromatin organization and gene expression control (3, 7). Many of the affected signaling pathways have been shown to be mechanosensitive, making the separation of the mechanical and gene expression models somewhat artificial.

While no curative treatment exists, interfering with the pathophysiological molecular effects of lamin mutants presents a promising target. The MAPK cascade (including p38 α , JNK, and ERK 1/2) is abnormally activated in mutant cardiomyocytes. Inhibiting MAPK components or mTOR has been shown to improve the phenotype in mouse models of laminopathic cardiomyopathies, and clinical trials for a p38 inhibitor are ongoing (8).

Acknowledgments

Research in the Wickström laboratory is supported by Helsinki Institute of Life Science, Wihuri Research Institute, Max Planck Society, and the German Research Foundation Deutsche Forschungsgemeinschaft through SFB 829 A11. Y.A. Miroshnikova is supported by the European Molecular Biology Organization Long-Term Fellowship ALTF 728-2017.

The authors declare no competing financial interest.

1. de Leeuw, R., et al. 2018. *Trends Cell Biol.* 28:34–45.
2. Gruenbaum, Y., and R. Foisner. 2015. *Annu. Rev. Biochem.* 84:131–164.
3. Kirby, T.J., and J. Lammerding. 2018. *Nat. Cell Biol.* 20:373–381.
4. van Steensel, B., and A.S. Belmont. 2017. *Cell.* 169:780–791.
5. Andrés, V., and J.M. González. 2009. *J. Cell Biol.* 187:945–957.
6. Dialynas, G., et al. 2015. *PLoS Genet.* 11:e1005231.
7. Miroshnikova, Y.A., et al. 2017. *J. Cell Sci.* 130:2243–2250.
8. Bonne, G., and A. Muchir. 2017. Cardiomyopathy Caused by Mutations in Nuclear A-Type Lamin Gene. <https://doi.org/10.5772/65315>

¹Helsinki Institute of Life Science, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland; ²Wihuri Research Institute, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland; ³Paul Gerson Unna Group "Skin Homeostasis and Ageing" Max Planck Institute for Biology of Ageing, Cologne, Germany.

*Y.A. Miroshnikova and T. Hammesfahr contributed equally to this paper; Correspondence to Sara A. Wickström: sara.wickstrom@helsinki.fi.

© 2019 Miroshnikova et al. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).