JCB Journal of Cell Biology

SPOTLIGHT

Long live lamins

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Mutations in genes encoding nuclear lamins cause diseases called laminopathies. In this issue, Hasper et al. (https://doi.org/10.1083/jcb.202307049) show that lamin A/C and the prelamin A variant in Hutchinson-Gilford progeria syndrome have relatively long lifetimes in affected tissues.

The nuclear lamina is a meshwork of non-canonical intermediate filaments on the inner aspect of the inner nuclear membrane (1). In mammals, three genes encode the lamin building blocks of the lamina. Mutations in these genes, particularly *LMNA* encoding prelamin A and lamin C, cause a wide range of tissue-selective diseases called laminopathies (2). Prelamin A is a precursor protein that is farnesylated at its carboxyl-terminus after synthesis. It then undergoes a series of posttranslational processing reactions, including proteolytic cleavage of the farnesylated carboxyl-terminus, to become mature lamin A that incorporates into the lamina.

In the laminopathy Hutchinson-Gilford progeria syndrome (HGPS), a heterozygous C-to-T transition in exon 11 of *LMNA* (*LMNA*$^{G608G/+}$) activates a cryptic RNA splice-donor site producing an internally truncated prelamin A variant called progerin that lacks the proteolytic cleavage site and remains farnesylated (3, 4). Individuals with HGPS have growth retardation and suffer from pathology primarily affecting bone, skin, subcutaneous fat, and the vascular system. Death usually occurs in the second decade of life from myocardial infarctions secondary to obstructive coronary artery disease. However, the coronary artery pathology in HGPS differs from the lipid-laden plaques in typical atherosclerosis, with major defects occurring in arterial vascular smooth muscle.

Considerable research has shown that farnesylated progerin and unprocessed prelamin A are "toxic" in certain cells. Pioneering experiments using protein farnesyltransferase inhibitors in progeroid mouse models (5, 6) led to human clinical trials and the subsequent approval of lonafarnib for the treatment of HGPS and processing-deficient progeroid laminopathies in which progerin or unprocessed prelamin A accumulate. However, it is not a definitive cure.

Despite their significance in pathology, extremely little is known about the regulation of lamin gene expression or the turnover of the proteins and disease-causing variants. In this issue, Hasper et al. (7) use several approaches including a technique called turnover and replication analysis by isotope labeling (TRAIL) to define the lifetimes of lamin A/C in different tissues of mice, as well as progerin in the *Lmna*$^{G609G/+}$ mouse model of HGPS (Fig. 1). TRAIL quantifies protein stability in vivo in animals fed chow containing ^{15}N by tracking the rate of incorporation of ^{15}N-labeled amino acids into the proteome by mass spectrometry in extracts of tissues isolated at different times. It also corrects for varying degrees of cell division and death. The authors show that relative to each tissue's proteome, lamin A/C are long-lived proteins with half-lives in the top decile and that the lifetimes of these proteins are longer in aorta, heart, and fat compared to liver and intestine in both wild-type and *Lmna*$^{G609/+}$ mice. Progerin also appears to be more long-lived than lamin A/C in the cardiovascular system, and its accumulation over time is associated with slower turnover of other abundant proteins. Intriguingly, the cardiovascular system is prominently affected in HGPS whereas the liver and intestine are not.

Hasper et al. (7) used innovative approaches to provide new fundamental information clearly showing that lamin A/C and progerin are relatively long-lived proteins and that their half-lives vary in different tissues. They further provided correlative evidence that the different turnover times may depend on differences in the extractability of the proteins from the nuclear envelope. However, the study has limitations and the authors' speculations about the findings to disease pathology require more experimental proof.

A notable limitation of the study is that it did not account for cell-type heterogeneity within tissues. In the adult murine heart, for example, only approximately half the cells are cardiomyocytes, with other prominent types being endothelial cells, vascular smooth muscle cells, and fibroblasts (8). There are even significant differences between cardiomyocyte populations in the heart, such as between those in atria or ventricles (9). Hence, the assessment of protein turnover in whole hearts begs for an analysis in individual cell types of this organ, in which the turnover rates could dramatically differ. A finding from one mouse genetic study could challenge the predicted half-life of lamin A/C in heart estimated by TRAIL. That study utilized adult mice with

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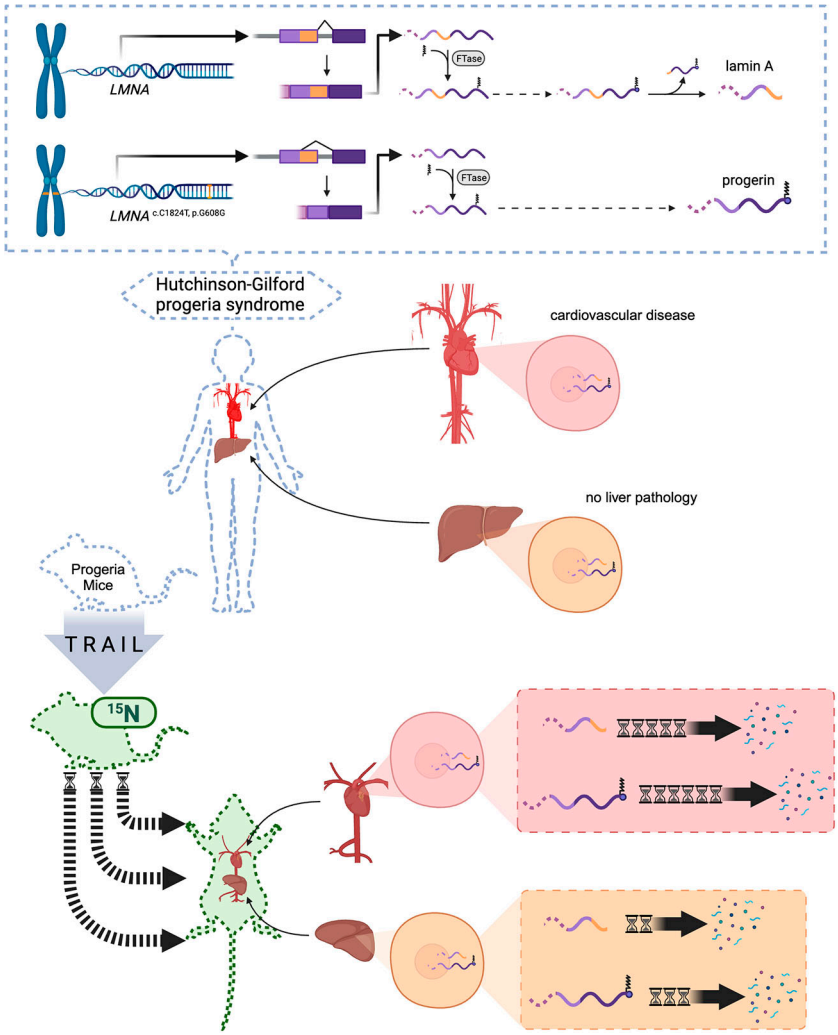

Figure 1. **Lamin half-life determination using TRAIL.** *LMNA* encodes prelamin A, which is farnesylated by protein farnesyltransferase (FTase). It then undergoes processing, including cleavage of the farnesylated carboxyl-terminus, to yield lamin A. A *LMNA* C1,824T (pG608G) HGPS mutation activates a splice site, leading to expression of progerin that cannot be fully processed and remains farnesylated. In HGPS, the cardiovascular system is affected whereas tissues such as liver are not. Hasper et al. (7) used TRAIL to measure ^{15}N-labeled protein turnover and determined that half-lives of lamin A/C and progerin are longer in affected tissues of progeria mice. Created with https://BioRender.com.

homozygous floxed *Lmna* alleles carrying a cardiomyocyte-specific transgene from which Cre expression could be induced by a single injection of tamoxifen; following Cre induction, the mice died within 3–4 wk (10). A lamin A/C half-life of ∼3 wk predicted by TRAIL in whole heart extracts must be reconciled with this finding given that heterozygous *Lmna* knockout mice have long lifespans. If lamin A/C indeed has a 3-wk half-life in cardiomyocytes, it would imply that active synthesis of the proteins, or other unknown essential RNA products of the gene, must occur in these cells for their function, even if the pre-existing proteins are only partly depleted.

The cellular heterogeneity in the heart is also relevant to cardiovascular pathology in HGPS. In HGPS, the myocardium is primarily damaged by ischemic injury secondary to coronary artery disease. Hence, measurement of progerin half-life in smooth muscle vascular cells of the aorta or the coronary arteries within the heart would be much more relevant than in whole heart. Unfortunately, Hasper et al. (7) were not able to thoroughly assess the aortas of *Lmna*$^{G609G/+}$ mice using TRAIL because of limited sample availability.

The implications of the relatively long lamin protein lifetimes for laminopathy therapies are unclear. Even if progerin does not completely turn over for a few months in the vascular system, most patients with HGPS live into the second decade. Those with other laminopathies, such as dilated cardiomyopathy or partial lipodystrophy, may have normal lifespans with good medical care. Therefore, it does not seem important for therapy if lamin A/C or disease-associated variants turn over in a few days or a few months. If lamins "accumulate damage, misfold, or irreversibly aggregate over time" to contribute to pathology as Hasper et al. (7) speculate, drugs that block farnesylation of only newly synthesized proteins would likely be ineffective, in contrast the beneficial effects of protein farnesyltransferase inhibitors in HGPS model mice (6). There are only scant data connecting lamin aggregates to pathology in HGPS or any other laminopathy.

The finding that lamins are relatively long-lived proteins with variable half-lives in different tissues is an important initial discovery. It should pave the way for measurements in single cell types that may differentially contribute to pathology in complex tissues. However, measurements of lamin A/C or variant protein turnover will likely provide only one piece of the complex puzzle of how mutations in *LMNA* cause tissue-selective laminopathies.

Acknowledgments

H.J. Worman is supported by the National Institutes of Health (R01AR048997, R01AG064944, R01HL159389, R01AG075047).

Disclosures: H.J. Worman has received consulting income from Eiger BioPharmaceuticals.

References

1. Turgay, Y., et al. 2017. *Nature*. https://doi.org/10.1038/nature21382
2. Shin, J.Y., and H.J. Worman. 2022. *Annu. Rev. Pathol.* https://doi.org/10.1146/annurev-pathol-042220-034240
3. Eriksson, M., et al. 2003. *Nature*. https://doi.org/10.1038/nature01629
4. De Sandre-Giovannoli, A., et al. 2003. *Science*. https://doi.org/10.1126/science.1084125
5. Fong, L.G., et al. 2006. *Science*. https://doi.org/10.1126/science.1124875
6. Yang, S.H., et al. 2006. *J. Clin. Invest.* https://doi.org/10.1172/JCI28968
7. Hasper, J., et al. 2024. *J. Cell Biol.* https://doi.org/10.1083/jcb.202307049
8. Souders, C.A., et al. 2009. *Circ. Res.* https://doi.org/10.1161/CIRCRESAHA.109.209809
9. Litviňuková, M., et al. 2020. *Nature*. https://doi.org/10.1038/s41586-020-2797-4
10. Chai, R.J., et al. 2021. *Nat. Commun.* https://doi.org/10.1038/s41467-021-24849-4