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Commentary

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17. Salomon, B., et al. 2000. B7/CD28 costimulation is essential for the homeostasis of the $CD4^+CD25^+$ immunoregulatory T cells that control autoimmune diabetes. *Immunity*. **12**:431–440.
18. Arif, S., et al. 2004. Autoreactive T cell responses show proinflammatory polarization in diabetes but a regulatory phenotype in health. *J. Clin. Invest.* **113**:451–463. doi:10.1172/JCI200419585.
19. Cobbold, S.P., et al. 2003. Regulatory T cells and dendritic cells in transplantation tolerance: molecular markers and mechanisms. *Immunol. Rev.* **196**:109–124.
20. Barrat, F.J., et al. 2002. In vitro generation of interleukin 10-producing regulatory $CD4^+$ T cells is induced by immunosuppressive drugs and inhibited by T helper type 1(Th1)-and Th2-inducing cytokines. *J. Exp. Med.* **195**:603–616.
21. Herold, K.C., et al. 2003. Activation of human T cells by FcR nonbinding anti-CD3 mAb, hOKT3γ1(Ala-Ala). *J. Clin. Invest.* **111**:409–418. doi:10.1172/JCI200316090.
22. Salek-Ardakani, S., Arrand, J.R., and Mackett, M. 2002. Epstein-Barr virus encoded interleukin-10 inhibits HLA-class I, ICAM-1, and B7 expression on human monocytes: implications for immune evasion by EBV. *Virology*. **304**:342–351.

How do mutations in lamins A and C cause disease?

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Mutations in lamins A and C, nuclear intermediate-filament proteins in nearly all somatic cells, cause a variety of diseases that primarily affect striated muscle, adipocytes, or peripheral nerves or cause features of premature aging. Two new studies (see the related articles beginning on pages 357 and 370) use lamin A/C–deficient mice, which develop striated muscle disease, as a model to investigate pathogenic mechanisms. These reports provide evidence for a stepwise process in which mechanically stressed cells first develop chromatin and nuclear envelope damage and then develop secondary alterations in the transcriptional activation of genes in adaptive and protective pathways.

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The nuclear lamina is a meshwork of intermediate filaments, primarily localized on the inner aspect of the inner nuclear membrane, that forms from polymerization of proteins called lamins (1–3). In humans, two genes encode B-type lamins, which are constitutively expressed in somatic cells. *LMNA* (*Lmna* in mice) encodes developmentally regulated A-type lamins, including the major somatic cell isoforms lamins A and C (4).

Since 1999, mutations in *LMNA* have been shown to cause several different inherited diseases (Table 1). Some, such as Emery-Dreifuss muscular dystrophy (EDMD) and Dunnigan-type familial partial lipodystrophy (FPLD), are rather tissue-specific (5). Others, such as Hutchinson-Gilford progeria syndrome, which is caused by a unique mutation in lamin A (6, 7), are more generalized. Before these discoveries, the predominant functions of lamins A and C were thought to be to provide mechanical support to the nucleus and to anchor "silent" heterochromatin to the inner nuclear membrane. The discoveries linking lamins A and C to inherited disorders have led to a new question: How do mutations in these proteins, expressed in nearly all differentiated somatic cells, cause different diseases, some of which are tissue-specific?

Mechanical stress versus gene expression

Investigators in the field have proposed two nonexclusive hypotheses to address this question. The "mechanical stress" hypothesis states that abnormalities in nuclear structure, which result from lamin mutations, lead to increased susceptibility to cellular damage by physical stress. This hypothesis is supported by observations that fibroblasts from patients with lamin A/C mutations and transfected cells expressing the mutant pro-

Table 1
Diseases caused by mutations in lamins A and C

Striated muscle diseases (cardiomyopathy with variable skeletal muscle involvement)
Autosomal dominant Emery-Dreifuss muscular dystrophy (no. 181350)
Autosomal recessive Emery-Dreifuss muscular dystrophy (no. 604929)
Cardiomyopathy dilated 1A (no. 115200)
Limb-girdle muscular dystrophy type 1B (no. 159001)
Partial lipodystrophy syndromes (with or without developmental abnormalities)
Dunnigan-type familial partial lipodystrophy (no. 151660)
Lipoatrophy with diabetes, hepatic steatosis, hypertrophic cardiomyopathy, and leukomelanodermic papules (no. 608056)
Mandibuloacral dysplasia (no. 248370)
Peripheral neuropathy
Charcot-Marie-Tooth disorder type 2B1 (no. 605588)
Premature aging syndromes
Hutchinson-Gilford progeria syndrome (no. 176670)
Atypical Werner syndrome (no. 277700 for Werner syndrome)

Additional information and original references can be found within ref. 5 and at the Online Mendelian Inheritance in Man database (OMIM; ref. 19). OMIM entry numbers are given in parentheses.

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Nonstandard abbreviations used: Emery-Dreifuss muscular dystrophy (EDMD); Dunnigan-type familial partial lipodystrophy (FPLD).

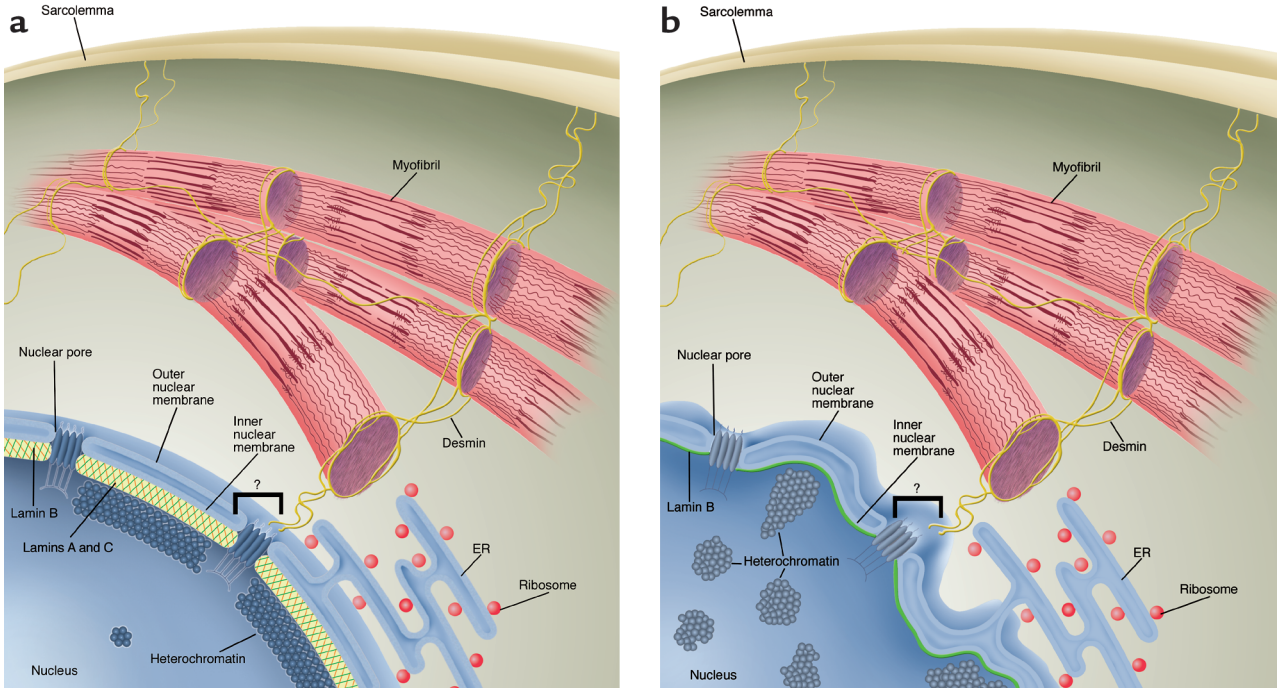

Figure 1
Schematic diagrams showing nuclear envelopes of a normal myocyte (**a**) and a myocyte from a mouse lacking lamins A and C (**b**). The nuclear envelope contains the inner nuclear membrane, pore membranes, and the outer nuclear membrane, which is directly continuous with the endoplasmic reticulum (ER). It also contains the nuclear lamina and nuclear pore complexes. The nuclear lamina of a normal myocyte (**a**) is composed of A-type (lamins A and C) and B-type (lamin B) lamins, which form a meshwork of intermediate filaments (yellow, red, and green). At the periphery of the nucleus, heterochromatin is preferentially associated with the inner nuclear membrane and the lamina. Putative connections (? in figure) may exist between cytoplasmic desmin filaments and the external faces of the nuclear pore complexes. In a myocyte of a lamin A/C–deficient mouse (**b**), the lamina is composed of only B-type lamins (green), and the nuclear envelopes are irregularly shaped with morphological abnormalities. Nikolova et al. (14) showed that heterochromatin is largely relocated from the nuclear envelope to the interior, which could cause alterations in gene expression. They also showed changes in desmin localization and hypothesized that this may result from alterations of its putative association (? in figure) with the nuclear envelope. Using fibroblasts from lamin A/C–deficient mice, Lammerding et al. (15) showed that nuclear deformities are increased by applied mechanical strain with resultant defective mechanotransduction and attenuated expression of mechanoresponsive genes. Adapted with permission from the Massachusetts Medical Society, Copyright 2000 (20). All rights reserved.

teins often have severe abnormalities in nuclear morphology and that fibroblasts from subjects with FPLD are susceptible to damage by heat shock (6–12). The "gene expression" hypothesis, which proposes that the nuclear envelope plays a role in tissue-specific gene expression that can be altered by mutations in lamins, is based primarily on observed interactions between nuclear envelope and chromatin components.

A paucity of affected tissue from human subjects with "laminopathies" has limited the ability to test these hypotheses. This has been partially overcome by the ground-breaking work of Colin Stewart and collaborators (13), who generated a lamin A/C knockout mouse. While heterozygous mice are apparently normal, homozygous null mice develop cardiac abnormalities and regional skeletal myopathy that resemble human EDMD. Fibroblast nuclei from these mice also show structural alterations similar to those from affected human subjects. Thus, despite the fact that most patients with autosomal dominant EDMD have missense mutations, small deletions, or, rarely, haploinsufficiency of lamins A and C, the lamin A/C–deficient mouse is a useful model to study the disease. Two articles in this issue of the *JCI* (14, 15) use these mice to test the mechanical-stress and gene-expression hypotheses.

Impaired nuclear mechanics leading to alterations in gene expression

Nikolova et al. (14) carefully analyzed lamin A/C–deficient mice and showed that they develop dilated cardiomyopathy with an impairment of physiological hypertrophy. They showed that nuclei of cardiac tissue and isolated myocytes have abnormal nuclear architecture with fragmented centromeric heterochromatin relocated from the periphery to the interior of the nucleus, and they correlated these alterations with possible defects in nucleocytoplasmic transport and gene expression. They also observed changes in desmin localization and speculated that a cellular skeleton integrating cytoplasmic desmin and nuclear lamina networks at the nuclear pore complexes is altered (Figure 1). Although there is no evidence for connections between the lamina and desmin networks in vivo, the strength of this study is the demonstration of impressive changes in chromatin structure, which may indeed have pathological consequences. In

general, there is a correlation between gene activity and nuclear location with genes physically localized near the periphery of the nucleus being inactive (16). Dynamic changes in gene activation may also occur during cellular differentiation, with silenced genes preferentially shifted to the nuclear periphery, close to centromeric heterochromatin, and activated ones translocated to a more central, euchromatic environment (17). A similar chromatin-reorganizing mechanism may normally be operative in nuclei of differentiating myoblasts or as a protective response in differentiated myocytes; loss of lamins A and C may disrupt this, leading to inappropriate gene activation or repression and resultant myopathy.

Lammerding et al. (15) directly explored nuclear mechanics and mechanotransduction in cultured embryonic fibroblasts from lamin A/C–deficient mice. Although connective tissue is not obviously abnormal in these mice, fibroblasts have misshaped nuclei with ultrastructural damage, validating the use of this cell type. Using magnetic-bead microrheology, the authors showed that the cytoplasm and nucleus have decreased stiffness in lamin A/C–deficient fibroblasts. They further showed that, in response to applied mechanical strain, these fibroblasts have increased nuclear deformations (Figure 1), defective mechanotransduction, attenuated expression of mechanosensitive genes activated by NF-κB, and diminished viability. Cytokine-stimulated NF-κB transcriptional activation was also attenuated.

These two studies (14, 15) suggest that impaired nuclear mechanics and secondary alterations in gene expression may cause striated muscle damage in subjects with certain lamin A/C mutations. By preferentially affecting transcriptional responses to mechanical stress or possibly other signals in nonmuscle cells, different mutations in lamins A and C may generate a diversity of tissue-specific pathological phenotypes. More generalized phenotypes, such as premature-aging syndromes, may result from mutations that cause more global abnormalities in chromatin structure and transcriptional control, much as classical Werner syndrome may result from mutations in a DNA helicase (18). Since the puzzling variety of diseases caused by mutations in lamins A and C has generated such a flurry of speculations as to pathogenic mechanisms (including our own work), it is refreshing to see solid experimental data that address this matter in this issue of the *JCI*.

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1. Aebi, U., Cohn, J., Buhle, L., and Gerace, L. 1986. The nuclear lamina is a meshwork of intermediate-type filaments. *Nature*. **323**:560–564.
2. McKeon, F.D., Kirschner, M.W., and Caput, D. 1986. Homologies in both primary and secondary structure between nuclear envelope and intermediate filament proteins. *Nature*. **319**:463–468.
3. Fisher, D.Z., Chaudhary, N., and Blobel, G. 1986. cDNA sequencing of nuclear lamins A and C reveals primary and secondary structural homology to intermediate filament proteins. *Proc. Natl. Acad. Sci. U. S. A.* **83**:6450–6454.
4. Lin, F., and Worman, H.J. 1993. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. *J. Biol. Chem.* **268**:16321–16326.
5. Worman, H.J., and Courvalin, J.-C. 2002. The nuclear lamina and inherited disease. *Trends Cell Biol.* **12**:591–598.
6. Eriksson, M., et al. 2003. Recurrent *de novo* point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*. **423**:293–298.
7. De Sandre-Giovannoli, A., et al. 2003. Lamin A truncation in Hutchinson-Gilford progeria. *Science*. **300**:2055.
8. Östlund, C., Bonne, G., Schwartz, K., and Worman, H.J. 2001. Properties of lamin A mutants found in Emery-Dreifuss muscular dystrophy, cardiomyopathy and Dunnigan-type partial lipodystrophy. *J. Cell Sci.* **114**:4435–4445.
9. Raharjo, W.H., Enarson, P., Sullivan, T., Stewart, C.L., and Burke, B. 2001. Nuclear envelope defects associated with *LMNA* mutations cause dilated cardiomyopathy and Emery-Dreifuss muscular dystrophy. *J. Cell Sci.* **114**:4447–4457.
10. Vigouroux, C., et al. 2001. Nuclear envelope disorganization in fibroblasts from lipodystrophic patients with heterozygous R482Q/W mutations in the lamin A/C gene. *J. Cell Sci.* **114**:4459–4468.
11. Holt, I., et al. 2003. Effect of pathogenic mis-sense mutations in lamin A on its interaction with emerin *in vivo*. *J. Cell Sci.* **116**:3027–3035.
12. Favreau, C., et al. 2003. Expression of lamin A mutated in the carboxyl-terminal tail generates an aberrant nuclear phenotype similar to that observed in cells from patients with Dunnigan-type partial lipodystrophy and Emery-Dreifuss muscular dystrophy. *Exp. Cell Res.* **282**:14–23.
13. Sullivan, T., et al. 1999. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. *J. Cell Biol.* **147**:913–920.
14. Nikolova, V., et al. 2004. Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C–deficient mice. *J. Clin. Invest.* **113**:357–369. doi: 10.1172/JCI200419448.
15. Lammerding, J., et al. 2004. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J. Clin. Invest.* **113**:370–378. doi:10.1172/JCI200419670.
16. Cremer, T., and Cremer, C. 2001. Chromosome territories, nuclear architecture and gene regulation in mammalian cells. *Nat. Rev. Genet.* **2**:292–301.
17. Brown, K.E., Baxter, J., Graf, D., Merkenschlager, M., and Fisher, A.G. 1999. Dynamic repositioning of genes in the nucleus of lymphocytes preparing for cell division. *Mol. Cell.* **3**:207–217.
18. Yu, C.E., et al. 1996. Positional cloning of the Werner's syndrome gene. *Science.* **272**:258–262.
19. Online Mendelian Inheritance in Man, OMIM. 2000. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University. Baltimore, Maryland, USA; National Center for Biotechnology Information, National Library of Medicine. Bethesda, Maryland, USA. http://www.ncbi.nlm.nih.gov/omim/.
20. Dalakas, M.C., et al. 2000. Desmin myopathy, a skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene. *N. Engl. J. Med.* **342**:770–780.