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Aging and nuclear organization: lamins and progeria

Leslie C Mounkes and Colin L Stewart[1]

The discoveries of at least eight human diseases arising from mutations in *LMNA*, which encodes the nuclear A-type lamins, have revealed the nuclear envelope as an organelle associated with a variety of fundamental cellular processes. The most recently discovered diseases associated with *LMNA* mutations are the premature aging disorders Hutchinson–Gilford progeria syndrome (HGPS) and atypical Werner's syndrome. The phenotypes of both HGPS patients and a mouse model of progeria suggest diverse compromised tissue functions leading to defects reminiscent of aging. Aspects of the diseases associated with disrupted nuclear envelope/lamin functions may be explained by decreased cellular proliferation, loss of tissue repair capability and a decline in the ability to maintain a differentiated state.

Addresses
Cancer and Developmental Biology Laboratory, NCI at Frederick, PO Box B, Frederick, Maryland, 21702 USA
[1]e-mail: stewartc@ncifcrf.gov

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Abbreviations

EDMD	Emery–Dreifuss muscular dystrophy
FPLD	familial partial lipodystrophy
HGPS	Hutchinson–Gilford progeria syndrome
IF	intermediate filament
INM	inner nuclear membrane
Ins/Igfr	insulin/insulin-like growth factor
LMNA	lamin A gene
MAD	mandibuloacral disease
NE	nuclear envelope

Introduction

Aging and death are inevitable in the life cycles of organisms. An understanding of why we age and the processes underlying aging has been a subject of much debate and research over the centuries. Within the past decade considerable progress has been made in determining which physiological processes influence longevity. An emerging consensus is that aging is a consequence of macromolecular damage by reactive oxygen species, which oxidize lipids, proteins and, in particular, DNA, with damage to the latter leading to mutations and chromosomal abnormalities [1]. These changes cause the malfunction of cellular organelles, particularly mitochondria, resulting in cell and tissue degeneration.

Genetically tractable organisms, especially those having a relatively short lifespan, such as the worm *Caenorhabditis elegans*, *Drosophila* and the yeast *Saccharomyces cerevisiae*, have been useful in determining the biochemical and molecular bases of longevity. Neuroendocrine pathways, in particular the insulin/insulin-like growth factor (Ins/Igfr) pathway, are central to regulating longevity in multicellular animals and may well be significant in mammals [2]. The role of the Ins/Igfr pathway in regulating metabolism and longevity is also consistent with the observation that caloric restriction prolongs lifespan [3] and that the NAD/oxidative phosphorylation pathway may influence the activity of the histone deacetylase, *Sir2*, which regulates longevity in yeast [4].

Humans are clearly less amenable to such genetic manipulation. However, two rare congenital diseases, Hutchinson–Gilford progeria syndrome (HGPS) and Werner's Syndrome, have attracted much interest, primarily because of their resemblance to an accelerated aging process.

Here we review the recent findings that mutations in the A-type lamins are responsible for HGPS and some cases of atypical Werner's syndrome. These findings, together with recent studies on cells lacking the A-type lamins that demonstrate a role for the lamins in regulating signaling pathways, chromatin organization and the mechanical integrity of the nucleus, reveal new aspects of the functional organization of the nucleus and how alterations to the lamins may relate to certain processes in aging.

The progerias

HGPS is a rare, dominantly inherited disease caused by mutations in *LMNA*, the gene coding for the A-type lamins [5••,6••]. Patients show symptoms of premature aging, including severe growth retardation, loss of subcutaneous fat, alopecia, reduced bone density and poor muscle development. The average age of death in HGPS is 12–15 years, usually by myocardial infarction or stroke [7]. However, patients do not show any increase in tumor susceptibility, cataract formation or cognitive degeneration, features often associated with normal aging, and HGPS has therefore been referred to as a segmental progeroid syndrome, as it only partially reproduces the aging process [8]. The majority of HGPS cases are associated with a splicing defect in exon 11 of the *LMNA* gene, resulting in the Lamin A protein lacking 50 amino acids of the carboxy-terminal globular domain [6••,9]. This

shortened form of the Lamin A protein has been tentatively assigned the name Progerin.

A second premature aging disease is Werner's syndrome. In the majority of patients (83%), Werner's is inherited as an autosomal recessive disease due to mutations in *WRN*, a 3′–5′RecQ DNA helicase-exonuclease that unwinds DNA and cleaves nucleotides from DNA termini [10]. Patients with the disease show a high incidence of early-onset cataracts, arthrosclerosis, diabetes, premature graying of hair and early death, usually in their late 40s. Unlike HGPS, Werner's syndrome is associated with an increased risk of neoplasms [11], although the mean age of death (47 years) in Werner's is much older than in HGPS, which possibly allows the accumulation of mutations that might enhance the risk of unchecked cell growth.

A subset of Werner's syndrome patients are known as atypical cases, because they do not carry detectable mutations in the *WRN* gene. A recent report revealed that 15% of these atypical patients had missense mutations in the *LMNA* gene resulting in amino acid substitutions either in the amino-terminal globular domain or the heptad repeats of the Lamin rod domain [12••].

The lamins

The lamins are type-V intermediate filament (IF) proteins located in the nucleus, primarily in the nuclear periphery, underlying the nuclear envelope. The lamins consist of the A and B types. Both types share the structural features of having a small globular domain at the amino terminus and a larger globular domain at the C terminus, separated by a rod domain of α-helical coiled coils [13]. A largely undeciphered process of dimerization, multimerization and higher-order assembly produces a network of lamin IFs, which comprise the 20–50 nm-thick nuclear lamina. The nuclear lamina structurally supports the nuclear envelope (NE) and largely determines the overall shape of the interphase nucleus [14]. In addition, the lamina associates with chromatin both directly and indirectly and has been implicated in the regulation of gene expression and in DNA synthesis [15].

Two separate genes, *LMNB1* and *LMNB2*, encode the B-type lamins [16], whereas A-type lamins arise by alternative splicing of the single *LMNA* gene on human chromosome 1 [17]. In *LMNA* the first 566 amino acids are common to both lamins A and C. Lamin A has an additional 98 amino acids at the carboxy terminus, whereas Lamin C has only six unique carboxy amino acids. Both lamins A and C appear to be incorporated into the nuclear lamina at relatively equivalent ratios. A-type and B-type lamins differ in their expression patterns during development and in certain adult cell types [18,19], as well as in their behavior during disassembly and reassembly of the NE during cell division [20]. A series of post-translational modifications facilitate the assembly of lamin A and B-type lamins into the lamina. Lamin A and the B-type lamins are farnesylated at a CaaX motif (where C is cysteine, a is any amino acid with an aliphatic side chain and X is any amino acid) in the carboxyl terminus. This lipid moiety results in the insertion of the lamins into the inner nuclear membrane. Subsequent cleavage produces a mature membrane-bound form of the lamin proteins. Lamin C, which lacks a farnesylation site, relies on the prior incorporation of Lamin A for its inclusion into the nuclear lamina [21,22].

Lamins and disease

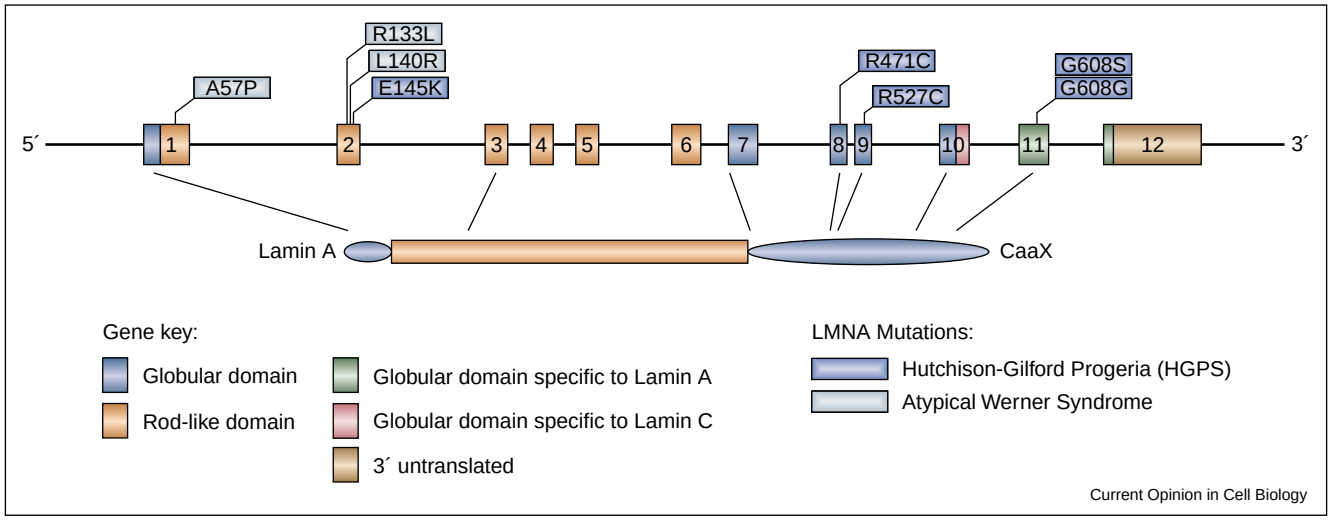
One of the more remarkable findings in the study of the nuclear lamina over the past four years has been the discovery that different, predominantly missense mutations in the *LMNA* gene result in at least eight clinically definable diseases, many of which affect specific tissues [23]. To date these diseases have been grouped into two broad classes. The first group comprises those affecting striated muscles, both skeletal and cardiac, and includes Emery–Dreifuss muscular dystrophy (EDMD), limb-girdle muscular dystrophy 1B (LGMD-1B) and dilated cardiomyopathy (DCM). The second group of diseases affects white fat deposition and bone turnover and includes familial partial lipodystrophy (FPLD) and mandibuloacral disease (MAD). A sixth disease, the neuropathy Charcot-Marie-Tooth type 2B1 (CMT2B1), results in demyelination of peripheral motor nerves. To these diseases are now added the progeric aging diseases: HGPS and some cases of atypical Werner's syndrome.

A mouse model for HGPS was derived by the introduction of a splicing defect in intron 9 in the mouse *Lmna* gene, which leads to a set of phenotypes closely resembling the human disease [24••]. Loss of subcutaneous fat, decreased bone density, poor muscle development and growth retardation are some of the most striking features of the mouse model. In addition, the mice die prematurely by four weeks of age and have craniofacial deformities and other skeletal abnormalities similar to both MAD and HGPS [24••]. The extent to which these phenotypes reflect a normal aging process is unclear, but the overall similarities in terminal phenotypes of mouse and man is striking. Cataracts, senility and increased incidence of tumors are characteristics of aging not observed in either HGPS patients or the progeric mutant mice for reasons that are not apparent. Attempts at making a mouse model for typical Werner's syndrome have been unsuccessful, despite a 70% sequence homology between the human and mouse genes [25,26]. However the murine Wrn protein is diffusely distributed throughout the nucleus, whereas human WRN protein is primarily restricted to the nucleolus [27] (see Figure 1).

Disease mechanisms

Because the A-type lamins are expressed in the majority of adult cells and tissues, with the exception of some stem

Figure 1



The distribution of mutations in the *LMNA* gene that result in HGPS and atypical Werner's syndrome are shown in relation to the gene and protein structure. The most common HGPS-causing mutation is the splicing mutation at G608 in exon 11.

cell populations, much interest and speculation has focused on how different *LMNA* mutations distributed throughout the gene result in such diverse tissue-specific diseases, including progeria. Several models have been proposed to account for this puzzle. These models are not, however, mutually exclusive, and it is possible that multiple mechanisms may account for the various pathologies [23].

Mice carrying engineered mutations in *Lmna* and cells from patients with one of several laminopathies, including the progerias, reveal dramatic defects in nuclear envelope structure. The nuclei show frequent blebbing or 'herniations', including large-scale alterations in nuclear shape, increased separation of the inner and outer nuclear membranes, clustering of nuclear pores, loss of some inner nuclear membrane (INM) proteins from one pole of the nucleus and disruption of the underlying electron-dense heterochromatin [14,23,28].

On the basis of these observations, the suggestion arose that nuclei containing defective lamins may be mechanically more fragile than their wild-type counterparts and that this fragility may ultimately lead to nuclear damage and cell death. Nuclei assembled *in vitro* in the absence of lamins are more prone to breakage than nuclei assembled in the presence of a full complement of lamins, and nuclear envelopes from $Lmna^{-/-}$ mice exhibit increased fragility [14,29]. Direct analysis of the mechanical properties of the $Lmna^{-/-}$ fibroblast nuclei in response to physical stretching of the cells revealed that the nuclei were indeed less rigid than normal wild-type nuclei [30]. Surprisingly, the cytoplasm of the $Lmna^{-/-}$ cells was also less 'stiff,' indicating that the rigidity of the cytoplasmic cytoskeleton is intimately tied to the state of the nuclear envelope/lamina. The $Lmna^{-/-}$ fibroblasts also showed diminished activation of the NF-κB pathway and were more prone to apoptosis and necrosis than normal fibroblasts when subjected to repetitive mechanical stress [30]. This evidence for enhanced nuclear fragility is particularly attractive as an explanation for the cardiac and skeletal muscle pathologies as the forces generated during muscle contraction could potentially lead to preferential breakage of nuclei containing a defective nuclear lamina. Nuclei in non-contractile tissues might remain relatively unaffected despite displaying abnormal nuclear organization. Similarly, effects on the mechanical integrity of nuclei may help explain the susceptibility of HGPS patients to arthrosclerosis and cardiovascular disease [31], as much evidence has indicated that mechanical weakening of the vascular endothelial and smooth-muscle cells may be the initial pathological event leading to arthrosclerosis [32].

Future studies will need to determine what effects the various mis-sense mutations have on the mechanical integrity of nuclei from different tissues. One particular mutation may more severely weaken the nuclei in cardiomyocytes than the same mutation in myotubes. Mechanical stress as a factor in the development of FPLD, MAD and perhaps many of the tissues affected in HGPS appears to be a less attractive explanation, as it is highly unlikely that adipocyte and bone nuclei are subjected to forces comparable to those encountered in muscle.

A complication to understanding the basis of the different disease mechanisms is that significant fractions (10–25%)

of fibroblasts from FPLD patients exhibit nuclear structural changes [33] very similar to those seen in the dystrophic *Lmna*-null mice, which however do not have FPLD [34]. In fact a more careful analysis found that even 5% of normal cells show blebbing. If these alterations in nuclear morphology are present at some basal level in all tissue (cell) types, and so long as the number of cells affected is small, there may be no overt phenotype. However, it may still be the case that in for example progeria the number of affected cells is significantly increased, resulting in a laminopathy. Disruption of the lamina and its associated proteins may affect other cellular processes, such as signaling pathways, including the NF-κB pathway as described above [30], or possibly the TGF-β/Smad pathways [35]. In addition, the mutations could disrupt interactions between the lamins and chromatin or other nuclear proteins. Indeed it has been suggested that mutations in the carboxy globular domain that cause FPLD and MAD are due to perturbations in the interactions between Lamin A and other proteins, such as the cholesterol synthesis regulator SREBP1 [36–38].

The effects Progerin has on the NE and how this aberrant form of Lamin A can wreak so much havoc in individuals remains to be determined. Structural predictions suggest that the 50-amino-acid deletion may affect post-translational modifications required for A-type lamin integration into the INM and lamina. By contrast, Lamin C would be unaffected as its termination codon occurs before the truncation, although any effect on A-type lamin integration into the INM may compromise Lamin C integration [22]. Preliminary data suggest that Progerin is able to integrate into the lamina, although Progerin is present at a low level compared to the levels of intact full length Lamin A still produced [6••]. The effects of the *LMNA* mutations associated with atypical Werner's, apart from their effects on NE morphology, have not been established [12••]. There is also some dispute as to whether all the individuals with atypical Werner's develop HGPS, or whether their disease only partially resembles HGPS, as it has been suggested these patients may have some modified form of FPLD [39–41]. However, additional evidence for aberrant post-translational processing of the Lamins, resulting in disease, has come from mice deficient in the metalloproteinase gene *Zmpste24*. Zmpste24 is responsible for the proteolytic post-translational modification to Lamin A following farnesylation. Mice lacking *Zmpste24* are defective in prelamin A processing and exhibit post-natal growth retardation, skeletal abnormalities, muscle weakness and premature death, similar to some of the pathologies associated with lamin deficiency and progeria [42•,43•]. An individual diagnosed with MAD was also found to have a mutated *ZMPSTE24* allele [44].

NE components are also essential for proper cell proliferation and mitosis. Disruption of the lamins, and of other NE components such as BAF (barrier to autointegration factor), Emerin and Man1, all result in abnormal mitosis, chromosomal segregation and cell death [45,46]. Fibroblast cultures from HGPS patients appear to have a reduced rate of proliferation, altered expression levels of genes regulating the cell cycle and a slight increase in aneuploidy [47,48]. In the mouse model for HGPS, primary embryonic fibroblasts from D13 embryos consistently show a pattern of proliferation that, both in the long and the short term, is indistinguishable from that of wild-type fibroblasts. However, fibroblasts from different tissues of three-to-four-week-old postnatal HGPS mice do not proliferate in culture and rapidly die, whereas the same cell lines from normal mice do proliferate [24••]. This raises the possibility that growth retardation and delayed maturation in some of the tissues in HGPS may arise as a result of a postnatal defect in cell proliferation. These observations also suggest the existence of a developmentally mediated mechanism directing how cells proliferate in response to a defect in the lamins.

Conclusions

Progeria in humans is caused by mutations in either of the genes for Lamin A or in the Werner's RecQ DNA helicase. Much indirect evidence has suggested that other experimentally induced premature aging phenotypes are induced by inhibiting the DNA repair process [1]. The WRN helicase interacts directly with DNA, although how mutant forms of the protein result in progeria is not understood [10]. The identification of Progerin and other mutant forms of the Lamins as a cause of progeria has only recently been established. A full understanding of the biochemical and molecular functions of the lamins in the nucleus is still lacking. Only recently have some of the nuclear proteins with which the lamins interact been identified (e.g. emerin), and their functions need to be fully established as well. There is already much evidence indicating that the lamins have multiple functions within the nucleus in organizing chromatin, maintaining nuclear shape and regulating DNA synthesis [15]. It however remains to be determined what role the lamins have in maintaining genome integrity and possibly DNA repair mechanisms, which, when perturbed, may result in progeria and aging [49].

Analyzing the consequences of the lamin mutations in cells has provided some clues as to how progeria develops. The structural role of the lamins in maintaining nuclear stiffness, revealing that cells deficient in the A-type lamins are more susceptible to physical stress, may compromise the cells that make up the cardiovascular system — a highly mechanically stressed set of tissues. Furthermore, the derivation of a mouse model provides a valuable resource: preliminary studies have suggested that mutant forms of *Lmna* that cause progeria may act by altering cell proliferation, possibly by affecting mitosis. Such a defect would clearly affect tissue growth and repair.

There are also striking similarities between some of the laminopathies and both the physical and metabolic aspects of aging in the 21st century. Some of the physical consequences of aging, such as a reduction in muscle mass (sarcopenia), bone loss and redistribution of fat, are found in the laminopathies. Furthermore, the increasing scourge of a western lifestyle, Syndrome X or metabolic syndrome, which is characterized by obesity, fat redistribution, diabetes and dyslipidemia, is also strikingly similar to some of the laminopathies [50]. Together, these findings suggest that proper expression and function of the lamins play a key role in maintaining cell and tissue integrity during aging. Work aimed at improving our understanding of the molecular and biochemical functions of the lamins is clearly warranted.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Hasty P, Campisi J, Hoeijmakers J, van Steeg H, Vijg J: **Aging and genome maintenance: lessons from the mouse?** *Science* 2003, **299**:1355-1359.

2. Partridge L, Gems D: **Mechanisms of ageing: public or private?** *Nat Rev Genet* 2002, **3**:165-175.

3. Koubova J, Guarente L: **How does calorie restriction work?** *Genes Dev* 2003, **17**:313-321.

4. Bitterman KJ, Medvedik O, Sinclair DA: **Longevity regulation in *Saccharomyces cerevisiae*: linking metabolism, genome stability, and heterochromatin**. *Microbiol Mol Biol Rev* 2003, **67**:376-399.

5. •• De Sandre-Giovannoli A, Chaouch M, Kozlov S, Vallat JM, Tazir M, Kassouri N, Szepetowski P, Hammadouche T, Vandenberghe A, Stewart CL *et al.*: **Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot- Marie-Tooth disorder type 2) and mouse**. *Am J Hum Genet* 2002, **70**:726-736.
See annotation to [6••].

6. •• Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P *et al.*: **Recurrent *de novo* point mutations in lamin A cause Hutchinson–Gilford progeria syndrome**. *Nature* 2003, **423**:293-298.
These two papers show for the first time that mutations in the *LMNA* gene are responsible for the rare premature aging disease HGPS.

7. Sarkar PK, Shinton RA: **Hutchinson–Guilford progeria syndrome**. *Postgrad Med J* 2001, **77**:312-317.

8. Martin GM, Oshima J: **Lessons from human progeroid syndromes**. *Nature* 2000, **408**:263-266.

9. De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M *et al.*: **Lamin A truncation in Hutchinson–Gilford progeria**. *Science* 2003, **300**:2055.

10. Oshima J: **The Werner syndrome protein: an update**. *Bioessays* 2000, **22**:894-901.

11. Mohaghegh P, Hickson ID: **DNA helicase deficiencies associated with cancer predisposition and premature ageing disorders**. *Hum Mol Genet* 2001, **10**:741-746.

12. •• Chen L, Lee L, Kudlow BA, Dos Santos HG, Sletvold O, Shafeghati Y, Botha EG, Garg A, Hanson NB, Martin GM *et al.*: **LMNA mutations in atypical Werner's syndrome**. *Lancet* 2003, **362**:440-445.
This paper shows that other mutations in the *LMNA* gene can also result in the rare premature aging disease HGPS. It raises questions as to how the mutant forms of these lamins result in the disease, compared to the more common splicing variant.

13. Stuurman N, Heins S, Aebi U: **Nuclear lamins: their structure, assembly, and interactions**. *J Struct Biol* 1998, **122**:42-66.

14. Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Bhat N, Nagashima K, Stewart CL, Burke B: **Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy**. *J Cell Biol* 1999, **147**:913-920.

15. Goldman RD, Gruenbaum Y, Moir RD, Shumaker DK, Spann TP: **Nuclear lamins: building blocks of nuclear architecture**. *Genes Dev* 2002, **16**:533-547.

16. Hoger TH, Zatloukal K, Waizenegger I, Krohne G: **Characterization of a second highly conserved B-type lamin present in cells previously thought to contain only a single B-type lamin**. *Chromosoma* 1990, **99**:379-390.

17. Lin F, Worman HJ: **Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C**. *J Biol Chem* 1993, **268**:16321-16326.

18. Stewart C, Burke B: **Teratocarcinoma stem cells and early mouse embryos contain only a single major lamin polypeptide closely resembling lamin B**. *Cell* 1987, **51**:383-392.

19. Broers JL, Machiels BM, Kuijpers HJ, Smedts F, van den Kieboom R, Raymond Y, Ramaekers FC: **A- and B-type lamins are differentially expressed in normal human tissues**. *Histochem Cell Biol* 1997, **107**:505-517.

20. Burke B, Ellenberg J: **Remodelling the walls of the nucleus**. *Nat Rev Mol Cell Biol* 2002, **3**:487-497.

21. Izumi M, Vaughan OA, Hutchison CJ, Gilbert DM: **Head and/or CaaX domain deletions of lamin proteins disrupt preformed lamin A and C but not lamin B structure in mammalian cells**. *Mol Biol Cell* 2000, **11**:4323-4337.

22. Vaughan A, Alvarez-Reyes M, Bridger JM, Broers JL, Ramaekers FC, Wehnert M, Morris GE, Whitfield WGF, Hutchison CJ: **Both emerin and lamin C depend on lamin A for localization at the nuclear envelope**. *J Cell Sci* 2001, **114**:2577-2590.

23. Burke B, Stewart CL: **Life at the edge: the nuclear envelope and human disease**. *Nat Rev Mol Cell Biol* 2002, **3**:575-585.

24. •• Mounkes LC, Kozlov S, Hernandez L, Sullivan T, Stewart CL: **A progeroid syndrome in mice is caused by defects in A-type lamins**. *Nature* 2003, **423**:298-301.
The derivation of a mouse model for HGPS is described. The mutation causing progeria in the mouse is different from the human mutations, although the similarity in phenotype is striking. The mouse mutation again raises questions as to how the different A-type lamin mutant proteins cause progeria.

25. Lebel M, Leder P: **A deletion within the murine Werner syndrome helicase induces sensitivity to inhibitors of topoisomerase and loss of cellular proliferative capacity**. *Proc Natl Acad Sci U S A* 1998, **95**:13097-13102.

26. Lombard DB, Beard C, Johnson B, Marciniak RA, Dausman J, Bronson R, Buhlmann JE, Lipman R, Curry R, Sharpe A *et al.*: **Mutations in the WRN gene in mice accelerate mortality in a p53-null background**. *Mol Cell Biol* 2000, **20**:3286-3291.

27. Marciniak RA, Lombard DB, Johnson FB, Guarente L: **Nucleolar localization of the Werner syndrome protein in human cells**. *Proc Natl Acad Sci U S A* 1998, **95**:6887-6892.

28. Muchir A, van Engelen BG, Lammens M, Mislow JM, McNally E, Schwartz K, Bonne G: **Nuclear envelope alterations in fibroblasts from LGMD1B patients carrying nonsense Y259X heterozygous or homozygous mutation in lamin A/C gene**. *Exp Cell Res* 2003, **291**:352-362.

29. Newport JW, Wilson KL, Dunphy WG: **A lamin-independent pathway for nuclear envelope assembly**. *J Cell Biol* 1990, **111**:2247-2259.

30. Lammerding J, Schulze CP, Takahashi T, Kozlov S, Sullivan T, Kamm RD, Stewart CL, Lee RT: **Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction**. *J Clin Invest* 2004, **113** in press.

31. Hamer L, Kaplan F, Fallon M: **The musculoskeletal manifestations of progeria. A literature review**. *Orthopedics* 1988, **11**:763-769.

32. Davies PF, Barbee KA, Volin MV, Robotewskyj A, Chen J, Joseph L, Griem ML, Wernick MN, Jacobs E, Polacek DC *et al.*: **Spatial relationships in early signaling events of flow-mediated endothelial mechanotransduction**. *Annu Rev Physiol* 1997, **59**:527-549.

33. Vigouroux C, Auclair M, Dubosclard E, Pouchelet M, Capeau J, Courvalin JC, Buendia B: **Nuclear envelope disorganization in fibroblasts from lipodystrophic patients with heterozygous R482Q/W mutations in the lamin A/C gene**. *J Cell Sci* 2001, **114**:4459-4468.

34. Cutler DA, Sullivan T, Marcus-Samuels B, Stewart CL, Reitman ML: **Characterization of adiposity and metabolism in Lmna-deficient mice**. *Biochem Biophys Res Commun* 2002, **291**:522-527.

35. Osada S, Ohmori SY, Taira M: **XMAN1, an inner nuclear membrane protein, antagonizes BMP signaling by interacting with Smad1 in *Xenopus* embryos**. *Development* 2003, **130**:1783-1794.

36. Krimm I, Ostlund C, Gilquin B, Couprie J, Hossenlopp P, Mornon JP, Bonne G, Courvalin JC, Worman HJ, Zinn-Justin S: **The Ig-like structure of the C-terminal domain of lamin A/C, mutated in muscular dystrophies, cardiomyopathy, and partial lipodystrophy**. *Structure (Camb)* 2002, **10**:811-823.

37. Lloyd DJ, Trembath RC, Shackleton S: **A novel interaction between lamin A and SREBP1: implications for partial lipodystrophy and other laminopathies**. *Hum Mol Genet* 2002, **11**:769-777.

38. Dhe-Paganon S, Werner ED, Chi YI, Shoelson SE: **Structure of the globular tail of nuclear lamin**. *J Biol Chem* 2002, **277**:17381-17384.

39. Bonne G, Levy N: **LMNA mutations in atypical Werner's syndrome**. *Lancet* 2003, **362**:1585-1586.

40. Oshima J, Garg A, Martin GM, Kennedy BK: **LMNA mutations in atypical Werner's syndrome**. *Lancet* 2003, **362**:1586.

41. Vigouroux C, Caux F, Capeau J, Christin-Maitre S, Cohen A: **LMNA mutations in atypical Werner's syndrome**. *Lancet* 2003, **362**:1585.

42. • Bergo MO, Gavino B, Ross J, Schmidt WK, Hong C, Kendall LV, Mohr A, Meta M, Genant H, Jiang Y *et al.*: **Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect**. *Proc Natl Acad Sci U S A* 2002, **99**:13049-13054.
See annotation to [43•].

43. • Pendas AM, Zhou Z, Cadinanos J, Freije JM, Wang J, Hultenby K, Astudillo A, Wernerson A, Rodriguez F, Tryggvason K *et al.*: **Defective prelamin A processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice**. *Nat Genet* 2002, **31**:94-99.
These two papers show that defective post-translational processing of farnesylated proteins, including lamin A, results in mice with multiple pathologies, some of which are shared with the progeric mice. They suggest that processing of the lamins is may partly underlie the molecular basis of the progeric phenotype.

44. Agarwal AK, Fryns JP, Auchus RJ, Garg A: **Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia**. *Hum Mol Genet* 2003, **12**:1995-2001.

45. Zheng R, Ghirlando R, Lee MS, Mizuuchi K, Krause M, Craigie R: **Barrier-to-autointegration factor (BAF) bridges DNA in a discrete, higher-order nucleoprotein complex**. *Proc Natl Acad Sci U S A* 2000, **97**:8997-9002.

46. Liu J, Lee KK, Segura-Totten M, Neufeld E, Wilson KL, Gruenbaum Y: **MAN1 and emerin have overlapping function(s) essential for chromosome segregation and cell division in *Caenorhabditis elegans***. *Proc Natl Acad Sci U S A* 2003, **100**:4598-4603.

47. Mukherjee AB, Costello C: **Aneuploidy analysis in fibroblasts of human premature aging syndromes by FISH during *in vitro* cellular aging**. *Mech Ageing Dev* 1998, **103**:209-222.

48. Ly DH, Lockhart DJ, Lerner RA, Schultz PG: **Mitotic misregulation and human aging**. *Science* 2000, **287**:2486-2492.

49. Lieber MR, Ma Y, Pannicke U, Schwarz K: **Mechanism and regulation of human non-homologous DNA end-joining**. *Nat Rev Mol Cell Biol* 2003, **4**:712-720.

50. Björntop P: **Etiology of the Metabolic Syndrome**. In *Handbook of Obesity*. Edited by Bray GA, Bouchard C, James WPT: Dekker Inc.; 1998:573-600.