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# Nuclear lamins, diseases and aging

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Nuclear lamins are type V intermediate filament proteins. They are the major building blocks of the peripheral nuclear lamina, a complex meshwork of proteins underlying the inner nuclear membrane. In addition to providing nuclear shape and mechanical stability, they are required for chromatin organization, transcription regulation, DNA replication, nuclear assembly and nuclear positioning. Over the past few years, interest in the lamins has increased because of the identification of at least 12 distinct human diseases associated with mutations in the *LMNA* gene, which encodes A-type lamins. These diseases, collectively termed laminopathies, affect muscle, adipose, bone, nerve and skin cells and range from muscular dystrophies to accelerated aging.

## Addresses

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## Introduction: lamins are the intermediate filament proteins of the nucleus

Lamins are the main structural constituents of the nuclear lamina, a structure associated with the inner nuclear membrane [1], and are also present in the nucleoplasm [2]. They are members of the intermediate filament (IF) superfamily and are probably the ancestors of all IFs. Like all IFs, lamins have a characteristic tripartite organization comprising a short N-terminal head domain, a central  $\alpha$ -helical rod domain and a C-terminal globular tail domain (Figure 1a). Lamins are divided into A- and B-types on the basis of their protein structure and expression patterns. B-type lamins are encoded by distinct genes and are present in all metazoan cells, whereas A-type lamins are derived through alternative splicing of a single gene and are present only in differentiated cells of more complex organisms. The number of lamin genes and protein isoforms roughly correlates with the complexity of the

organism in which they are expressed [3]. However, the overall amino-acid sequence and structure of lamins is well conserved, including an immunoglobulin (Ig)-like fold motif in the lamin tail domain [4] (Figure 1c). All B-type lamins and lamin A are translated as pre-lamins with a C-terminal CaaX motif that is subject to three post-translational modifications. First the cysteine is farnesylated, then the last three residues (aaX) are cleaved off and subsequently the cysteine undergoes methyl esterification. While B-type lamins remain farnesylated, pre-lamin A undergoes a fourth maturation step in which the 15 C-terminal amino acids, including the farnesyl group, are cleaved off (Figure 2). Both cleavage steps in the maturation of lamin A are believed to be performed by a single zinc-metalloproteinase termed ZMPSTE24 (FACE-1) and are dependent on the sequence of processing steps [5]. The function of the farnesyl group is probably to target lamins to the nuclear membrane, either by direct interaction with the lipid membrane or by mediating a protein–protein interaction [6].

In the first part of this review we focus on the structural and functional aspects of nuclear lamins in diseases. The second part emphasizes the role of lamins in pre-mature as well as normal aging.

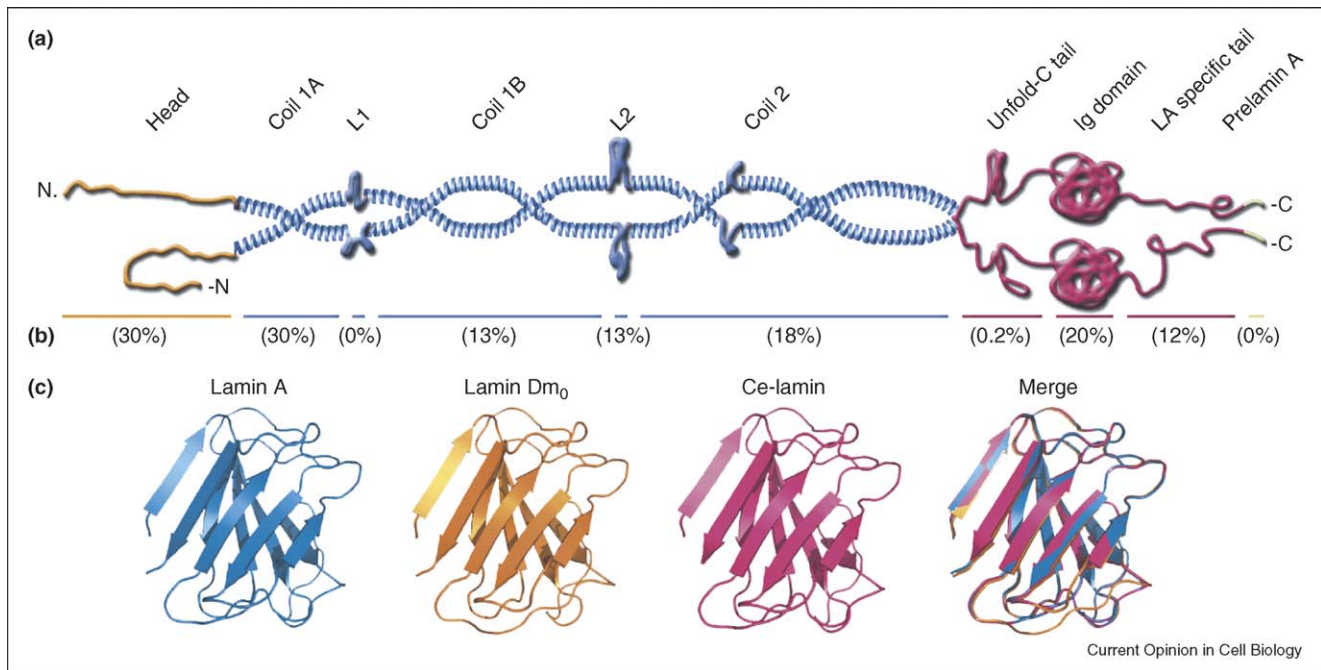
## The assembly of lamins into filaments occurs in distinct steps

In the *Xenopus* germinal vesicle, regions of the nuclear lamina are arranged as a tetragonal lattice of  $\sim 10$ -nm-wide filaments [7], although a similar organization has not been found in other cell types. *In vitro* assembly studies have shown that the basic subunit of the lamin polymer is a parallel dimer formed by coiled-coil interactions between the rod domains. These dimers further associate longitudinally through head-to-tail associations to make 2–3-nm-wide protofilaments [4,8\*]. These protofilaments form paracrystals, which are normally not observed *in vivo* [4]. A breakthrough in understanding lamin assembly *in vitro* was the formation of stable  $\sim 10$ -nm filaments of the *C. elegans* lamin that resemble the  $\sim 10$ -nm filament structure of cytoplasmic IFs, as well as the nuclear lamina of the germinal vesicles [9]. The Ce-lamin 10-nm filaments will help us to understand the role of lamin-binding proteins and the effect of disease-causing mutations on lamin filament assembly, which are challenging goals for future studies.

## Mutations in *LMNA* cause many heritable diseases

Currently there are no known human diseases associated with *LMNB1* or *LMNB2*. It is assumed that mutations in

Figure 1



Schematic presentation of the structure of lamins. **(a)** Schematic model of the structure of the lamin A dimer with the head domain depicted in orange, the rod domain depicted in blue, the C-terminal tail domain depicted in pink and the prelamin A-specific region in light green. The different sub-domains are indicated. Currently, only coil 2B and the Ig domain have been solved at atomic resolution [4]. **(b)** Frequency of mutated residues in the different sub-domains of human lamin A causing human heritable diseases. The data for (b) was obtained from the Leiden Muscular Dystrophy Pages ([http://www.dmd.nl/lmna\\_seqvar.html](http://www.dmd.nl/lmna_seqvar.html)). Interestingly, there is only one known disease-causing mutation associated with the unfolded tail domain, which binds the core histones [51]. **(c)** Comparison of the atomic model of the 105-residue Ig domain showing the evolutionary conservation between human lamins A/C, *Drosophila* lamin Dm<sub>0</sub> and *C. elegans* Ce-lamin.

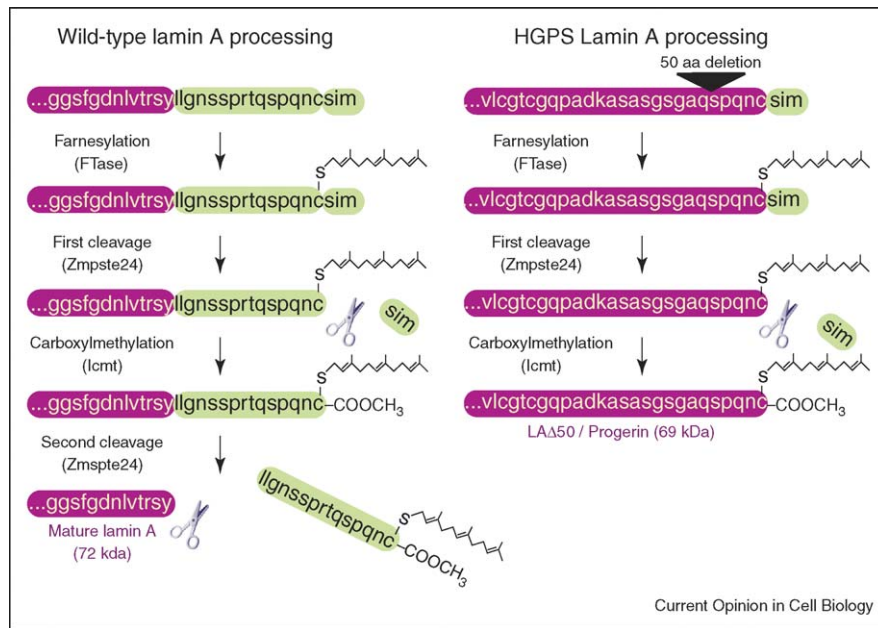
these genes are lethal, since downregulation of either *LMNB1* or *LMNB2* in HeLa cells causes apoptosis [10]. In contrast, >150 mutations in *LMNA* have been linked to various inherited diseases, called the 'laminopathies' [11,12]. These include diseases affecting muscle tissues (autosomal and recessive Emery Dreifuss muscular dystrophy [EDMD], autosomal dominant limb girdle muscular dystrophy and dilated cardiomyopathy, all of which include cardiac conduction defects), adipose tissues (autosomal dominant Dunnigan-type familial partial lipodystrophy and Seip syndrome), and axonal neurons (recessive Charcot-Marie-Tooth disorder type 2). Recently, the premature aging diseases Hutchinson Gilford progeria syndrome (HGPS), atypical Werner's syndrome and mandibuloacral dysplasia (MAD) have also been linked to mutations in *LMNA* [11,12]. Mutations in *LMNA* also cause the prenatal disease restrictive dermopathy (RD) [13<sup>\*</sup>] and complete loss of A-type lamins leads to prenatal lethality [14]. The disease-causing mutations are distributed essentially throughout the entire *LMNA* gene (Figure 1b) and the only disease for which mutations appear to cluster is partial lipodystrophy (~70% in the Ig fold). Also, some patients with a single mutation suffer multiple laminopathies [15], and the phenotype of any

given *LMNA* mutation can vary between individuals and between siblings. RD and accelerated aging diseases also appear in patients with mutations in the *ZMPSTE24* gene, encoding the lamin-A-processing metalloproteinase [13<sup>\*</sup>,16]. Mutations in genes encoding lamina-associated proteins (LAPs), including LBR, emerin, MAN1 and the non-membrane isoform of LAP2 (LAP2 $\alpha$ ), also cause heritable diseases similar to laminopathies [12,17].

How mutations in *LMNA* cause many different laminopathies is a major unanswered question. It has been hypothesized that lamin structures provide a scaffold that is used to sequester, assemble and regulate various protein complexes involved in nuclear integrity, gene expression, DNA replication, nuclear positioning and cell cycle progression [2,18]. On the basis of this hypothesis, several different models, which are not mutually exclusive, were proposed [12,19<sup>\*</sup>].

The first model takes into account the idea that one of the major functions of the nuclear lamina is to protect the structural integrity of the nucleus. According to this model, a mutant lamin A weakens the lamina structure and alters its mechanical properties, including resistance

Figure 2



Schematic diagram outlining the four steps of processing of prelamin A to mature lamin A. The first step involves farnesylation at the terminal cysteine by farnesyl transferase. The second step involves cleavage of the last three residues, probably by Zmpste24. The third step involves carboxymethylation of the terminal cysteine by Icmt, and the fourth step involves cleavage 15 amino acids away from the terminal cysteine by Zmpste24. In HGPS cells the second cleavage site of lamin A is missing as a result of deletion of 50 amino acids and the LAΔ50 (progerin) probably retains the farnesylated cysteine. B-type lamins undergo the first three steps but are not further processed (not shown).

to mechanical stress [20<sup>•</sup>,21]. In muscle cells in particular, this often leads to structural damage and cell death. In support of this model, fibroblasts derived from patients with different laminopathies frequently have abnormally shaped nuclei [22], and mouse fibroblasts lacking A-type lamins show increased nuclear fragility and impaired mechanical-stress-dependent gene expression *in vivo* [20<sup>•</sup>,21]. There is also some evidence that abnormal lamin assembly may destabilize the mechanical properties of cells and that this may be attributable to interactions between the nucleus and the cytoskeletal networks [23,24].

A second model proposes that A-type lamins and their associated proteins may be involved in regulating cell-type-specific gene expression [25]. Therefore, different mutations in *LMNA* can cause misregulation of different tissue-specific genes, either directly or at the epigenetic level. Candidate transcriptional regulators that interact with lamins and/or LAPs are germ cell-less, retinoblastoma protein, sterol response element binding protein-1, barrier to autointegration factor and OCT-1 [15,18]. However, the details of the molecular mechanisms underpinning this regulation remain unclear. The lamin-dependent regulation of specific genes could also occur through regulation of heterochromatin formation. In support of this, mouse fibroblasts lacking A-type lamins and fibroblasts from HGPS patients both exhibit a loss of

heterochromatin at the nuclear periphery [26<sup>••</sup>,27,28]. Additionally, alterations in epigenetic modifications regulating heterochromatin, such as histone methylation, have been observed in HGPS and MAD [29<sup>••</sup>,30,31].

Recently a third model proposed that A-type lamins play a role in cell proliferation, particularly in regulatory mechanisms controlling the cell cycle of adult stem cells [19<sup>•</sup>]. Support for this model comes from the observation that while embryonic muscle differentiation seems to be normal in EDMD patients, myoblasts expressing A-type lamins containing EDMD-causing mutations are unable to differentiate fully [32<sup>••</sup>,33].

### Lamins and aging

The two classical accelerated aging diseases are HGPS ('progeria of childhood') and Werner's syndrome ('progeria of adults'). HGPS symptoms usually become apparent in the first or second year of life and are characterized by sclerodermatous skin, hair loss, bone deformations, delayed dentition, growth retardation and loss of subcutaneous fat. The patients die between the ages of 13 and 20 years from atherosclerosis and cardiovascular disease. Most cases of HGPS result from a 1824C>T mutation (Gly608Gly) that creates an ectopic mRNA splicing site leading to the expression of a truncated pre-lamin A lacking 50 amino acids within its tail domain [34]. This mutant protein, which was termed LAΔ50 or progerin

[26<sup>••</sup>], lacks the second proteolytic cleavage site for the processing of lamin A and the mature protein contains eight residues of pre-lamin A and is presumably farnesylated (Figure 2). In addition to the 1824C>T mutation, there are reports of 10 other spontaneous dominant HGPS mutations in *LMNA* located in regions that encode the lamin A head domain, coil 1B, the Ig-fold domain and the non-Ig-fold C-terminal region in the tail domain (<http://www.umd.be:2000> and [http://www.dmd.nl/lmna\\_seqvar.html](http://www.dmd.nl/lmna_seqvar.html)). Three other dominant mutations causing accelerated aging phenotypes that appear in late childhood were characterized as atypical Werner's syndrome [35]. There is also a recessive form of HGPS caused by a 1626 G>C (Lys542Asn) mutation.

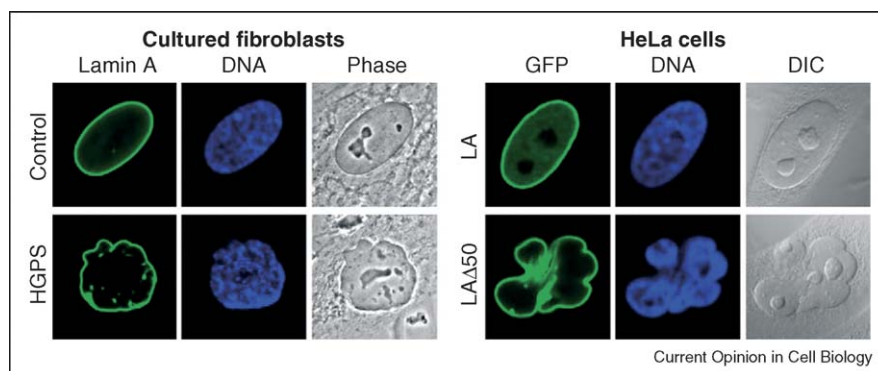
Cultured fibroblasts derived from HGPS patients have limited cell proliferation capacity and undergo early senescence [26<sup>••</sup>]. As these cells are propagated in culture, they undergo significant changes in nuclear shape (Figure 3), including lobulation of the nuclear envelope, thickening of the nuclear lamina, loss of peripheral heterochromatin and clustering of nuclear pore complexes (NPCs); all these nuclear changes correlate with an accumulation of LA $\Delta$ 50. The alterations in nuclear structure appear to be caused by a concentration-dependent dominant-negative effect of LA $\Delta$ 50, as expression of the mutant lamin in normal cells leads to similar nuclear phenotypes (Figure 3) [26<sup>••</sup>]. Silencing of the 1824C>T mutant mRNA has been reported to down-regulate LA $\Delta$ 50 expression [29<sup>••</sup>,36], with the result that nuclei in the affected cells exhibit a return to normal nuclear morphology, as reflected by a loss of nuclear lobulation, normal expression levels of nuclear lamina proteins, restoration of the normal pattern of the heterochromatin markers heterochromatin protein 1 and tri-methyl lysine 9 of core histone H3, and proper expression of several genes that were found to be misregulated in the untreated HGPS fibroblasts, including *MMP3*, *HAS3*, *TIM3*,

*MMP14* and *CCL8* [29<sup>••</sup>]. Interestingly, these global changes in nuclear and chromatin organization were not dependent on cell division. These results further support the hypothesis that LA $\Delta$ 50 affects nuclear structure and chromatin organization [29<sup>••</sup>,36]. However, the mechanisms through which lamins regulate chromatin are unknown. This is an area of great interest for future exploration.

The dominant negative effect of LA $\Delta$ 50 expression may be attributable to the farnesyl moiety retained at the C terminus as a result of the second proteolytic cleavage site involved in the processing of prelamin A being missing [37<sup>•</sup>] (Figure 2). Another evidence supporting this state of farnesylation comes from experiments showing that the shape of nuclei in cells expressing LA $\Delta$ 50 returns to normal following treatment with farnesyl transferase inhibitors (FTIs) [38<sup>•</sup>–40<sup>•</sup>]. In addition, treatment of HGPS fibroblasts with the FTI mevinolin in combination with the histone deacetylase inhibitor Trichostatin A (TSA) has been reported to restore normal heterochromatin organization [30]. These results suggest that FTIs may be useful for the treatment of HGPS patients. Interestingly, further data suggest that FTIs might also be useful in treating other laminopathies [40<sup>•</sup>,41<sup>•</sup>,42]. Some FTIs are already in phase II and III clinical trials and are well tolerated [41<sup>•</sup>]. However, the broad spectrum of farnesylated proteins within a cell that could be affected by these drugs, including all B-type lamins, might represent a double-edged sword.

It has also been shown that mutations in *Zmpste24* cause accumulation of farnesylated pre-lamin A in RD and MAD. These diseases share similar characteristics with HGPS [13<sup>•</sup>,16,43]. Additionally, mice deficient in *Zmpste24* have retarded growth, accelerated aging and other phenotypes observed in HGPS and other laminopathies [44–46]. Additional insight into the mechanisms

Figure 3



Cultured fibroblasts derived either from a healthy control individual (control) or from an HGPS patient (HGPS) were fixed with methanol and processed for indirect immunofluorescence microscopy using an antibody against Lamin A. HeLa cells expressing either GFP-Lamin A (LA) or GFP-LA $\Delta$ 50 (LA $\Delta$ 50) were fixed with methanol and processed for fluorescence microscopy. DNA was visualized with Hoechst dye. Confocal images are shown. Cells accumulating the mutant protein exhibit an abnormal, highly lobulated nuclear shape.

of accelerated aging comes from results showing that cells derived from either HGPS patients or from *Zmpste24*-null mice have abnormal responses to DNA damage and increased aneuploidy [47]. These cells are defective in recruiting the DNA repair factors 53PB1 and Rad51 to sites of DNA breaks, resulting in a delayed checkpoint response and defective DNA repair [47]. HGPS fibroblasts are also hypersensitive to heat-stress and exhibit an abnormal stress response [46,47]. Cells derived from *Zmpste24*-null mice have upregulated p53 target genes, indicating the existence of a checkpoint response of the stress signaling pathway that is affected by threshold levels of pre-lamin A [46]. Interestingly, the progeroid phenotypes could be partially rescued in mice that are both *Zmpste24*-null and *Lmna*-haploinsufficient individuals and in mice that are null for both *Zmpste24* and *p53* [46].

In *C. elegans*, the nuclear architecture in most non-neuronal cell types undergoes progressive stochastic (cell-by-cell) age-dependent alterations. Specifically, as normal worms age, the nuclei become lobulated and this is accompanied by changes in the organization of lamins, lamin-associated proteins, nucleoporins and peripheral heterochromatin [48\*\*]. These changes resemble those occurring in later-passage HGPS fibroblasts. Interestingly, the rate of the accumulation of these alterations is influenced by the insulin/IGF-1-like signaling pathway, which plays a major role in regulating the lifespan of worms [49]. For example, short-lived or long-lived insulin/IGF-1 mutants exhibited faster or slower rates of change in nuclear architecture, respectively [50].

## Conclusions

It is clear that nuclear lamins are essential components of nuclear architecture. Studies of their structure and function are now being facilitated through insights into the mechanisms causing the laminopathies known to be caused by a large number of mutations in *LMNA*.

Many interesting properties of the lamins remain to be determined. These include the structure of the different types of lamin assemblies both within the lamina and throughout the nucleoplasm, and the precise roles of the lamins in DNA replication and repair, in transcription, in the regulation of euchromatin-heterochromatin transitions, and in aging.

## Update

A recent study [52] provides surprising experimental evidences that mice lacking lamin A and prelamin A are entirely healthy. These mice generate lamin C only, have normal emerin localization, and exhibit very slight nuclear shape alterations. Therefore, both prelamin A and lamin A appear to be dispensable, at least in mice. The authors of this study speculate that this finding opens up new possibilities for treating human laminopathies, such as progeria. In another recent study [53], a transgenic

mouse carrying a human bacterial artificial chromosome, which expresses LAΔ50, was generated. This mouse develops progressive loss of vascular smooth muscle cells in the medial layer of large arteries, in a pattern very similar to that seen in children with HGPS. This is in agreement with the recent finding that an LAΔ50-specific antibody exhibits the strongest immunoreactivity in smooth muscle and endothelial cells of the vascular system of an HGPS patient [54]. Most recently it has been reported that lamin B is required for the formation of a matrix-like network essential for the assembly of the mitotic spindle [55\*\*]. The formation of this lamin B containing mitotic spindle matrix was shown to depend upon RanGTP, but not on the assembly of microtubules. Interestingly, several spindle assembly factors (SAFs) appear to associate with the spindle matrix in a lamin-B-dependent fashion.

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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. Stuurman N, Heins S, Aebi U: **Nuclear lamins: their structure, assembly, and interactions.** *J Struct Biol* 1998, **122**:42-66.
  2. Goldman RD, Gruenbaum Y, Moir RD, Shumaker DK, Spann TP: **Nuclear lamins: building blocks of nuclear architecture.** *Genes Dev* 2002, **16**:533-547.
  3. Erber A, Riemer D, Hofemeister H, Bovenschulte M, Stick R, Panopoulou G, Lehrach H, Weber K: **Characterization of the hydra lamin and its gene: a molecular phylogeny of metazoan lamins.** *J Mol Evol* 1999, **49**:260-271.
  4. Herrmann H, Aebi U: **Intermediate filaments: molecular structure, assembly mechanism, and integration into functionally distinct intracellular scaffolds.** *Annu Rev Biochem* 2004, **73**:749-789.
  5. Corrigan DP, Kuszczak D, Rusinol AE, Thewke DP, Hrycyna CA, Michaelis S, Sinensky MS: **Prelamin A endoproteolytic processing in vitro by recombinant Zmpste24.** *Biochem J* 2005, **387**:129-138.
  6. Hennekes H, Nigg EA: **The role of isoprenylation in membrane attachment of nuclear lamins. A single point mutation prevents proteolytic cleavage of the lamin A precursor and confers membrane binding properties.** *J Cell Sci* 1994, **107**:1019-1029.
  7. Aebi U, Cohn J, Buhle L, Gerace L: **The nuclear lamina is a meshwork of intermediate-type filaments.** *Nature* 1986, **323**:560-564.
  8. Strelkov SV, Schumacher J, Burkhard P, Aebi U, Herrmann H:
    - **Crystal structure of the human lamin A coil 2B dimer: implications for the head-to-tail association of nuclear lamins.** *J Mol Biol* 2004, **343**:1067-1080.

The crystal structure of the dimer coiled-coil of coil 2B from human lamin A at 2.2 Å resolution shows similar overall structure to vimentin. Mutations in this region that cause heritable disease are predicted to affect stages of filament assembly and lamina formation.

9. Karabinos A, Schunemann J, Meyer M, Aebi U, Weber K: **The single nuclear lamin of caenorhabditis elegans forms in vitro stable intermediate filaments and paracrystals with a reduced axial periodicity.** *J Mol Biol* 2003, **325**:241-247.
  10. Harborth J, Elbashir SM, Beichert K, Tuschl T, Weber K: **Identification of essential genes in cultured mammalian cells using small interfering RNAs.** *J Cell Sci* 2001, **114**:4557-4565.
  11. Hutchison CJ, Worman HJ: **A-type lamins: guardians of the soma?** *Nat Cell Biol* 2004, **6**:1062-1067.
  12. Worman HJ, Courvalin JC: **Nuclear envelope, nuclear lamina, and inherited disease.** *Int Rev Cytol* 2005, **246**:231-279.
  13. Navarro CL, Cadinanos J, Sandre-Giovannoli AD, Bernard R, Courrier S, Boccaccio I, Boyer A, Kleijer WJ, Wagner A, Giuliano F *et al.*: **Loss of ZMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of lamin A precursors.** *Hum Mol Genet* 2005, **14**:1503-1513.
- Mutations in the pre-lamin A cleaving enzyme ZMPSTE24 cause accelerated aging diseases similar to those associated with mutations in lamin A. Also described in [16,41\*,43].
14. 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.
  15. Zastrow MS, Vlcek S, Wilson KL: **Proteins that bind A-type lamins: integrating isolated clues.** *J Cell Sci* 2004, **117**:979-987.
  16. Agarwal AK, Fryns JP, Auchus RJ, Garg A: **Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia.** *Hum Mol Genet* 2003, **12**:1995-2001.
  17. Taylor MR, Slavov D, Gajewski A, Vlcek S, Ku L, Fain PR, Carniel E, Di Lenarda A, Sinagra G, Boucek MM *et al.*: **Thymopoietin (lamina-associated polypeptide 2) gene mutation associated with dilated cardiomyopathy.** *Hum Mutat* 2005, **26**:566-574.
  18. Gruenbaum Y, Margalit A, Shumaker DK, Wilson KL: **The nuclear lamina comes of age.** *Nat Rev Mol Cell Biol* 2005, **6**:21-31.
  19. Gotzmann J, Foisner R: **A-type lamin complexes and regenerative potential: a step towards understanding laminopathic diseases?** *Histochem Cell Biol* 2006, **125**:33-41.
- An excellent review of all known models for laminopathies, which also suggests the adult cell differentiation model for explaining laminopathies.
20. Lammerding J, Schulze PC, Takahashi T, Kozlov S, Sullivan T, Kamm RD, Stewart CL, Lee RS: **Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction.** *J Clin Invest* 2004, **113**:370-378.
- Evidence that *Imna*-null mouse embryo fibroblasts have deformed nuclei, impaired viability under mechanical stress, defective mechanotransduction and attenuated gene expression responses to mechanical stress via the NFκB signaling pathway.
21. Broers JL, Peeters EA, Kuijpers HJ, Endert J, Bouten CV, Oomens CW, Baaijens FP, Ramaekers FC: **Decreased mechanical stiffness in LMNA-/- cells is caused by defective nucleo-cytoskeletal integrity: implications for the development of laminopathies.** *Hum Mol Genet* 2004, **13**:2567-2580.
  22. Favreau C, Dubosclard E, Ostlund C, Vigouroux C, Capeau J, Wehnert M, Higuete D, Worman HJ, Courvalin JC, Buendia B: **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* 2003, **282**:14-23.
  23. Starr DA, Han M: **ANCHors away: an actin based mechanism of nuclear positioning.** *J Cell Sci* 2003, **116**:211-216.
  24. Wilhelmsen K, Litjens SH, Kuikman I, Tshimbalanga N, Janssen H, van den Bout I, Raymond K, Sonnenberg A: **Nesprin-3, a novel outer nuclear membrane protein, associates with the cytoskeletal linker protein plectin.** *J Cell Biol* 2005, **171**:799-810.
  25. Cohen M, Lee KK, Wilson KL, Gruenbaum Y: **Transcriptional repression, apoptosis, human disease and the functional evolution of the nuclear lamina.** *Trends Biochem Sci* 2001, **26**:41-47.
  26. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R *et al.*: **Accumulation of mutant lamin A causes progressive changes in nuclear architecture in hutchinson-gilford progeria syndrome.** *Proc Natl Acad Sci USA* 2004, **101**:8963-8968.
- Fibroblasts from Hutchinson–Gilford progeria patients show early senescence. Dramatic changes in nuclear structure, loss of peripheral heterochromatin and changes in nuclear envelope composition are observed. These changes can be also observed in normal cells that express LAΔ50.
27. Sullivan T, Escalante-Alcalde D, Bhatt H, Anver M, Naryan B, 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.
  28. Nikolova V, Leimena C, McMahon AC, Tan JC, Chandar S, Jogia D, Kesteven SH, Michalicek J, Otway R, Verheyen F *et al.*: **Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C-deficient mice.** *J Clin Invest* 2004, **113**:357-369.
  29. Scaffidi P, Misteli T: **Reversal of the cellular phenotype in the premature aging disease Hutchinson–Gilford progeria syndrome.** *Nat Med* 2005, **11**:440-445.
- Inhibition of progerin expression in HGPS fibroblasts by different anti-sense oligonucleotides causes reversal of all detectable cellular phenotypes. Similar observations appear in [36].
30. Columbaro M, Capanni C, Mattioli E, Novelli G, Parnaik VK, Squarzoni S, Maraldi NM, Lattanzi G: **Rescue of heterochromatin organization in Hutchinson–Gilford progeria by drug treatment.** *Cell Mol Life Sci* 2005, **62**:2669-2678.
  31. Filesi I, Gullotta F, Lattanzi G, D'Apice MR, Capanni C, Nardone AM, Columbaro M, Scarano G, Mattioli E, Sabatelli P *et al.*: **Alterations of nuclear envelope and chromatin organization in mandibuloacral dysplasia, a rare form of laminopathy.** *Physiol Genomics* 2005, **23**:150-158.
  32. Favreau C, Higuete D, Courvalin JC, Buendia B: **Expression of a mutant lamin A that causes emery-dreifuss muscular dystrophy inhibits in vitro differentiation of C2C12 myoblasts.** *Mol Cell Biol* 2004, **24**:1481-1492.
- Evidence that expression of EDMD mutations in myoblasts prevents these cells from differentiating *in vitro* into mature muscle cells. Similar observations also appear in reference [33].
33. Markiewicz E, Ledran M, Hutchison CJ: **Remodelling of the nuclear lamina and nucleoskeleton is required for skeletal muscle differentiation in vitro.** *J Cell Sci* 2005, **118**:409-420.
  34. 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.
  35. 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.
  36. Huang S, Chen L, Libina N, Janes J, Martin GM, Campisi J, Oshima J: **Correction of cellular phenotypes of Hutchinson–Gilford progeria cells by RNA interference.** *Hum Genet* 2005, **118**:444-450.
  37. Glynn MW, Glover TW: **Incomplete processing of mutant lamin A in Hutchinson–Gilford progeria leads to nuclear abnormalities, which are reversed by farnesyltransferase inhibition.** *Hum Mol Genet* 2005, **14**:2959-2969.
- Incubation of HGPS cells or cells expressing progerin with farnesyl transferase inhibitors causes reversal of the cellular phenotype. These studies [37–41\*] demonstrate that the farnesylated lamin A is toxic to cells and suggest a possible therapeutic treatment.
38. Capell BC, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, Conneely KN, Gordon LB, Der CJ, Cox AD, Collins FS: **Inhibiting farnesylation of progerin prevents the characteristic nuclear**

- blebbing of hutchinson-gilford progeria syndrome. *Proc Natl Acad Sci USA* 2005, **102**:12879-12884.  
See annotation to [37\*].**
39. Mallampalli MP, Huyer G, Bendale P, Gelb MH, Michaelis S:  
• **Inhibiting farnesylation reverses the nuclear morphology defect in a HeLa cell model for Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2005, **102**:14416-14421.  
See annotation to [37\*].**
40. Toth JI, Yang SH, Qiao X, Beigneux AP, Gelb MH, Moulson CL,  
• Miner JH, Young SG, Fong LG: **Blocking protein farnesyltransferase improves nuclear shape in fibroblasts from humans with progeroid syndromes. *Proc Natl Acad Sci USA* 2005, **102**:12873-12878.  
See annotation to [37\*].**
41. Young SG, Fong LG, Michaelis S: **Prelamin A, Zmpste24, misshapen cell nuclei, and progeria – new evidence suggesting that protein farnesylation could be important for disease pathogenesis. *J Lipid Res* 2005, **46**:2531-2558.  
See annotation to [37\*].**
42. Capanni C, Mattioli E, Columbaro M, Lucarelli E, Parnaik VK, Novelli G, Wehnert M, Cenni V, Maraldi NM, Squarzone S *et al.*: **Altered pre-lamin A processing is a common mechanism leading to lipodystrophy. *Hum Mol Genet* 2005, **14**:1489-1502.**
43. Navarro C, De Sandre-Giovannoli A, Bernard R, Boccaccio I, Boyer A, Genevieve D, Hadj-Rabia S, Gaudy-Marqueste C, Smith HS, Vabres P *et al.*: **Lamin A and ZMPSTE24 (FACE-1) defects cause nuclear disorganisation and identify restrictive dermopathy as a lethal neonatal laminopathy. *Hum Mol Genet* 2004, **13**:2493-2503.**
44. 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.**
45. 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 USA* 2002, **99**:13049-13054.**
46. Varela I, Cadinanos J, Pendas AM, Gutierrez-Fernandez A, Folgueras AR, Sanchez LM, Zhou Z, Rodriguez FJ, Stewart CL, Vega JA *et al.*: **Accelerated ageing in mice deficient in Zmpste24 protease is linked to p53 signalling activation. *Nature* 2005, **437**:564-568.**
47. Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, Huang JD, Li KM, Chau PY, Chen DJ *et al.*: **Genomic instability in laminopathy-based premature aging. *Nat Med* 2005, **11**:780-785.**
48. Haithcock E, Dayani Y, Neufeld E, Zahand AJ, Feinstein N,  
•• Mattout A, Gruenbaum Y, Liu J: **Age-related changes of nuclear architecture in caenorhabditis elegans. *Proc Natl Acad Sci USA* 2005, **102**:16690-16695.  
Motivated by alterations observed in HGPS fibroblasts, this study demonstrates that distinct progressive and stochastic changes in nuclear architecture of *C. elegans* occur during the normal aging process of this organism, primarily in non-neuronal cells including muscle and intestinal cells. These changes are influenced by mutations in the insulin/IGF-1-like signaling pathway.**
49. Guarente L, Kenyon C: **Genetic pathways that regulate ageing in model organisms. *Nature* 2000, **408**:255-262.**
50. Paradisi M, McClintock D, Boguslavsky RL, Pedicelli C, Worman HJ, Djabali K: **Dermal fibroblasts in Hutchinson–Gilford progeria syndrome with the lamin A G608G mutation have dysmorphic nuclei and are hypersensitive to heat stress. *BMC Cell Biol* 2005, **6**:27.**
51. Taniura H, Glass C, Gerace L: **A chromatin binding site in the tail domain of nuclear lamins that interacts with core histones. *J Cell Biol* 1995, **131**:33-44.**
52. Fong LG, Ng JK, Lammerding J, Vickers TA, Meta M, Cote N, Gavino B, Qiao X, Chang SY, Young SR *et al.*: **Prelamin A and lamin A appear to be dispensable in the nuclear lamina. *J Clin Invest* 2006, **116**:743-752.**
53. Varga R, Eriksson M, Erdos MR, Olive M, Harten I, Kolodgie F, Capell BC, Cheng J, Faddah D, Perkins S *et al.*: **Progressive vascular smooth muscle cell defects in a mouse model of Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2006, **103**:3250-3255.**
54. McClintock D, Gordon LB, Djabali K: **Hutchinson–Gilford progeria mutant lamin A primarily targets human vascular cells as detected by an anti-Lamin A G608G antibody. *Proc Natl Acad Sci USA* 2006, **103**:2154-2159.**
55. Tsai MY, Wang S, Heidinger J, Shumaker D, Adam SA, Goldman RD,  
•• Zheng Y: **A mitotic lamin B-matrix induced by RanGTP required for spindle assembly. *Science* 2006, **311**:1887-1893.  
This study demonstrates for the first time a direct role for the nuclear lamins in mitosis. Specifically, lamin B is required for the formation of a mitotic spindle matrix and for the association of several SAFs with this matrix. Both events are essential for the assembly of a functional mitotic spindle.**