Cellular Basis of Laminopathies

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The nuclear lamina is the main architectural component of a eukaryotic nucleus. More than an inert scaffold, the lamina is essential for maintaining proper nuclear organisation, epigenetic composition, transcriptional regulation and cell cycle progression. Mutations within lamin genes lead to a wide range of diseases known as laminopathies, among which the striking premature aging disease Hutchinson–Gilford progeria syndrome (HGPS) is the most well known. Studies regarding the cellular basis of laminopathies have advanced our knowledge of the nuclear lamina and yielded remarkable insights into the process of normal human aging. Understanding the molecular mechanisms responsible for disease manifestations has also led to the development of novel therapeutic strategies to address lamina-related diseases. Ultimately, scientists and clinicians seek to provide treatment options to laminopathy patients to alleviate symptoms and perhaps to cure these diseases in the future.

Introduction

The nucleus of eukaryotic cells can be functionally divided into two main parts: the nucleoplasm and the nuclear envelope (NE) (Dechat *et al*., 2008). The cell's nucleoplasm houses the chromosomes, nucleolus and a group of soluble nuclear proteins. The NE is a double lipid bilayer that acts as a physical barrier separating the chromosomes from the cytoplasm. Structurally, the NE consists of the nuclear pore complexes (NPCs), the outer nuclear membrane (ONM), the inner nuclear membrane (INM), the perinuclear space (30–50 nm wide lumen between the ONM and INM) and the nuclear lamina. The NPCs, found in areas where the ONM and INM fuse, allow for trafficking of macromolecules to and from the nucleus. The ONM connects to the rough endoplasmic reticulum, and the INM hosts a distinct set of integral membrane proteins, interacting with chromatin and nuclear lamina (Capell and Collins, 2006).

The nuclear lamina is a main structural component of the nucleus, locating underneath the INM. It is made of a network of filamentous proteins, known as nuclear lamins. The lamins belong to the type V intermediate filament family of proteins and are present in all metazoan organisms (Goldman *et al*., 1986). The lamina supports the nuclear structure, and plays a regulatory role in nuclear organisation, transcription and cell division. The critical functions of the lamina are highlighted by a wide range of human diseases (termed 'laminopathies') that are linked to over 180 mutations in genes encoding lamins.

Based on sequence homology, expression patterns and biochemical properties, the lamins are categorised into A- or B-type (Dechat *et al*., 2010). A-type lamins, including A, C, C2 and Δ10 isoforms, are encoded by the *LMNA* gene on chromosome 1q12.2–1q21.3. *LMNB1* on chromosome 5q23.2 and *LMNB2* on chromosome 19p13.3 encode B-type lamins, lamin B1 and lamin B2, respectively. B-type lamins are essential components of the mitotic spindle matrix (Tsai *et al*., 2006). **See also**: Nuclear Envelope and Lamins: Organization and Dynamics; The Cell Nucleus

Both A- and B-type lamins begin as prelamins with Ras-like *C*-terminal –CAAX motifs, where C is cysteine, A an aliphatic amino acid and X a variable. This –CAAX motif induces an ordered posttranslational modification process, in which every step depends on the previous one (Worman *et al*., 2009; Dechat *et al*., 2010). Modification begins with isoprenylation by the addition of a farnesyl group to the cysteine of the –CAAX box by the enzyme farnesyltrasferase. Next, the –AAX are removed by either one of the two AAX endopeptidases, Rce1 (Ras-converting enzyme 1) for B-type lamins or Zmpste24 (Zinc metalloprotease related to the Ste24 homologue in budding yeast)/FACE1 (farnesylated-proteins converting enzyme) for prelamin A. The remaining farnesylated cysteine is then carboxymethylated by Icmt (isoprenylcysteine carboxy methyltransferase). After this step, B-type lamins become fully mature (Goldman *et al*., 2002). Prelamin A undergoes one additional processing step that Zmpste24/FACE1 removes 15 amino acids from the C-terminus, including the

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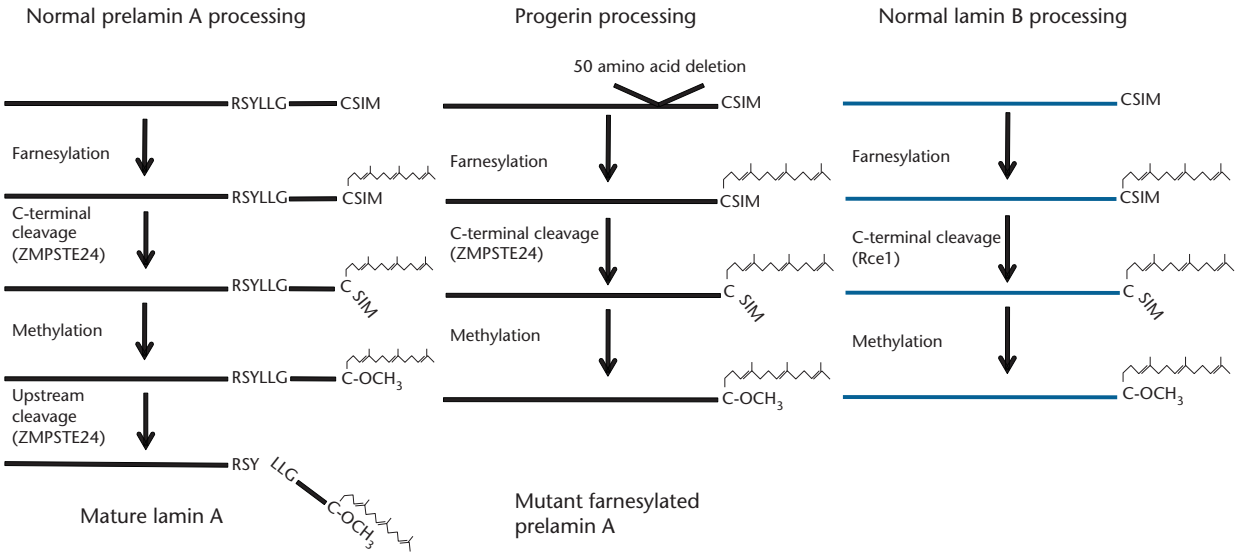

Figure 1 Lamin processing. Blue and black lines indicate different amino acid sequences.

farnesylated and methylated cysteine (Dechat *et al*., 2010). This final modification yields the mature form of lamin A (**Figure 1**).

Structurally, each lamin protein contains a short globular *N*-terminal 'head' domain, a central α helical rod domain, and a long globular *C*-terminal 'tail' domain (Dechat *et al*., 2010). Among these structural domains, of importance are the *C*-terminal 'tail' domains, where a highly conserved type s-immuno globuln-fold (Ig-fold) and the nuclear localisation signal reside (Loewinger and McKeon, 1998). *In vitro*, lamins are capable of self-assembly, in a stepwise manner, to form parallel coiled-coil dimmers, anti-parallel tetrameric protofilaments and 10 nm filaments (Dechat *et al*., 2010). *In vivo* studies have revealed that lamins A and B form separate filamentous networks with limited overlapping regions in the nuclear lamina (Shimi *et al*., 2008).

Laminopathies

Mutations in lamins are responsible for at least 16 different human diseases. Collectively known as laminopathies, these disease manifestations vary markedly in severity and phenotypic progression. On the basis of their most prominent clinical features, we group these lamin-related diseases into three categories: muscular dystrophies, lipodystrophies and systemic laminopathies, including cardiomyopathies and progeriod syndromes.

Muscular dystrophy

Type 2 Emery–Dreifuss muscular dystrophy (EDMD) is the first disease linked to a mutation in the *LMNA* gene (Bonne *et al*., 1999). The phenotypes of EDMD include muscle wasting, weakness, slowly progressive contractures and cardiomyopathy (Bonne *et al*., 1999). Interestingly, X-linked EDMD is caused by mutations in emerin, a gene located on chromosome Xq29 (Bione *et al*., 1994). Emerin is an INM-associated membrane protein, which interacts with A-type lamins. To date, several additional lamin-related muscular dystrophies have been reported, including dilated cardiomyopathy type 1A, Limb Girdle muscular dystrophy, congenital muscular dystrophy and 'heart–hand' syndrome.

Lipodystrophy

Patients with lipodystrophies demonstrate dramatic loss in adipose tissues. In some reported cases lipodystrophy patients also develop premature atherosclerosis. A total of 75% of the Dunnigan-type familial partial lipodystrophy (FPLD2) cases are caused by autosomal dominant missense mutation in the codon 482 in the *LMNA* gene (Capanni *et al*., 2003). This mutation alters the charge of the Ig-fold of lamins A and C (Worman *et al*., 2009), which likely leads to altered lamina interactions with the proteins regulating adipogenesis. For example, sterol response element-binding protein (SREBP1), a key player in adipocyte differentiation, binds to the *C*-terminal domain of lamin A (Capell and Collins, 2006). The potential disrupted interaction between SREBP1 and lamina due to the exon 8 mutations may contribute to adipocyte defects in FLPD2 and other laminopathies (Capell and Collins, 2006).

Interestingly, in a female case of laminopathy, the symptoms of type-A insulin resistance syndrome were present, but no clinical evidence of lipodystrophy was found (Young *et al*., 2005). Genetic testing revealed a mutation in codon 602 (G→A) of *LMNA*, leading to glycine to serine substitution in the *C*-terminal tail of lamin A. Further examination of the patient's fibroblasts revealed abnormal nuclear morphology and impaired activation of

the insulin signal transduction pathway. Specifically, both insulin receptor β subunit (IRβ) and insulin receptor substrate-1 (IRS-1) were phosphorylated in the basal state. Upon insulin treatment, both IRβ and IRS-1 remained phosphorylated, which inhibits the stimulation of the downstream molecular effectors, protein kinase B (Akt/PKB) and mitogen-activated protein kinase (extracellular-regulated kinase (ERK) 1/2). The authors implied that the hyperphosphorylated state of IRβ and IRS-1 could be because of the impaired activity of the serine/theronine kinase PKCα, which binds to lamin A (Young *et al*., 2005). However, the precise molecular mechanisms contributing to these events remain largely unclear.

Systemic laminopathies

Systemic laminopathies diseases encompass a wide range of symptoms including premature aging, lipodystrophy, skeletal abnormalities, growth retardation, hair loss and cardiovascular disease.

Identified only in Algerian families, Charcot-Marie-Tooth (CMT) disease type 2B1 is a systemic laminopathy. Patients with CMT exhibit muscles wasting and axonal neuropathy. CMT is caused by a homozygous missense substitution (R298C) in the *LMNA* gene, which lies in the conserved rod domain of A-type lamins. Little is known about the molecular mechanisms underlying the development peripheral neuropathy in these patients (De Sandre-Giovannoli *et al*., 2002; Capell and Collins, 2006).

Mandibular dysplasia (MAD) is another systemic laminopathy characterised by growth retardation, craniofacial anomalies, skeletal abnormalities, pigmentary skin changes, lipodystrophy and, in some cases, premature aging (Filesi *et al*., 2005). MAD is most often caused by an autosomal recessive mutation at codon 527, leading an arginine to histidine substitution (Novelli *et al*., 2002). This amino acid change occurs in the *C*-terminal domain and may lead to altered lamina interactions. Cells from MAD patient show nuclear shape abnormalities, accumulation of prelamin A and irregular lamina thickness (Lombardi *et al*., 2007). MAD patients express significantly higher levels of active matrix metalloproteinase 9 (MMP9), an enzyme involved in the extracellular matrix (ECM) remodelling. This over-activation of MMP9 could potentially contribute to exhaustion of bone marrow stem cells (Lombardi *et al*., 2008).

Hutchinson–Gilford progeria syndrome (HGPS) is another systemic laminopathy. HGPS is a rare premature aging disease that manifests in infancy as a failure to thrive. The tissue-restricted, aging-related phenotypes include hair loss, diminished subcutaneous fat, skeletal abnormalities and cardiovascular diseases. In approximately 90% of cases, a *de novo* point mutation (C1824T) in exon 11 of the *LMNA* gene is the cause of the disease. This nucleotide substitution does not lead to an amino acid substitution (G608G), but instead partially activates a cryptic splice donor site and causes an in-frame deletion of 150 base pairs within the prelamin A messenger ribonucleic acid (mRNA) (Eriksson *et al*., 2003; De Sandre-Giovannoli *et al*., 2003). This is subseqently translated into a mutant lamin A protein, known as progerin, with an internal deletion of 50 amino acids (residues 607–646). Like lamin A, progerin undergoes posttranslational processing (**Figure 1**). However, progerin remains farnesylated due to the absence of the internal amino acid cleavage site recognised by Zmpste24/FACE1 (Capell and Collins, 2006). Consequently, progerin has a dominant negative effect nuclear lamina organisation by interrupting essential cellular processes such as transcription, replication, deoxyribonucleic acid (DNA) damage repair, differentiation and cell division (Capell and Collins, 2006). Within all laminopathies, HGPS has the most dramatic phenotypes, recapitulating characteristics from each of the previously mentioned categories.

Defects in HGPS

Changes in nuclear shape

The nuclei of HGPS cells exhibit abnormal nuclear morphology, thickening of the nuclear lamina, clustering of NPCs and mislocalisation of some nuclear proteins (Goldman *et al*., 2004). The misshapen nuclei in HGPS cells typically contain blebs that are rich in lamin A/C but devoid of nuclear pores and lamin B (Goldman *et al*., 2004). Further characterisation showed that the nucleoplasm within the blebs contains open (i.e. euchromatic) chromatin (Dechat *et al*., 2010). The RNA polymerase Pol II and an active promotor mark H3K4me3 were both found to be enriched inside the blebs. However, further analysis via labelling of newly generated RNA transcripts and a histone marker for transcription elongation (H3K36me3) revealed that elongation of RNA transcripts is absent within the nuclear blebs (Shimi *et al*., 2008). Perhaps one reason for this phenomenon is the absence of NPCs in blebbed NE regions because some genes and gene regulators need to tether to the nuclear pores for proper functions (Scheider and Groschedl, 2007). The altered transcription and chromatin composition found in the nuclear blebs provides a small glimpse of how progerin impinges on the structure and function of the nuclear compartment as a whole.

Thickening of the nuclear lamina was first observed using transmission electron microscopy in HGPS cells, and can be attributed to the altered biochemistry in polymerisation of the nuclear lamina at the presence of progerin (Goldman *et al*., 2004). Studies using fluorescent green protein (GFP) tagged lamin A and progerin revealed that while wild-type lamins form distinct A- and B-type homopolymers, progerin integrates with both lamins B and A, disrupting the layout of the nuclear lamina (Delbarre *et al*., 2006). Moreover, progerin is permanently farnesylated, leading to defects in NE disassembly and reassembly during cell division (Cao *et al*., 2007; Dechat *et al*., 2007).

Altered protein interactions

It has been hypothesised that the potential changes in protein interactions of wild-type lamin A versus progerin may partially contribute to the various phenotypes in HGPS. In line with the abnormal clustering and mislocalisation of NPCs in HGPS, progerin showed decreased interactions with two nuclear pore-associated proteins: *Nup153* (which anchors NPCs to the nuclear lamina) and *Tpr* (which plays a role in the formation of heterochromatin-free zones near the nuclear pore complex). Additionally, progerin exhibited increased interactions with *PCNA* (proliferating cellular nuclear antigen) (Musich and Zou, 2009). A recent proteomics study identified distinct subsets of nuclear proteins that preferentially bind progerin over lamin A (Kubben *et al*., 2011). Moreover, a recent study demonstrated that expressions of various lamin A mutants associated with cardiomyopathies and muscular dystrophies lead to defective nuclear movement and positioning (Folker *et al*., 2011), suggesting lamin A plays a prominent role in mediating interactions between the nucleus and the cytoskeleton.

Misregulated epigenetic modifications and gene expression

The interactions between peripheral heterochromatin and nuclear lamina primarily take place between the lamin globular tail domains and the histone tails. In HGPS primary fibroblast cells, the accumulation of progerin leads to a global loss of peripheral heterochromatin and a decrease in repressive histone marks (Shumaker *et al*., 2006; Scaffidi and Misteli, 2005). Importantly, these epigenetic changes occur before the appearance of nuclear morphological abnormalities and may act as an upstream signal (Shumaker *et al*., 2006). A recent study revealed that progerin binds less efficiently to the histone H3 tail than wild-type lamin A (Bruston *et al*., 2010). The authors proposed that the amino acid sequence 607–646 in lamin A be crucial for proper interactions of lamina and chromatin. The loss of peripheral heterochromatin and its markers could be a result of progerin's inability to bind repressive histone tails.

Epigenetic changes may lead to altered gene expression. Furthermore, lamins also have significant roles in transcription regulation, since they interact with RNA polymerase II, RNA splicing factors and transcription regulators (Capell and Collins, 2006). Studies looking at gene expression patterns detected significant increases in satellite III (DNA sequences normally found within pericentric heterochromatin) transcripts in HGPS cells, revealing that normal epigenetic silencing of heterochromatin is altered in HGPS cells (Shumaker *et al*., 2006). Additionally, components of the transforming growth factor-β (TGFβ) superfamily, Wnt family, and NOTCH signalling pathways showed altered expression in HGPS mouse models. Moreover, human mesenchymal stem cells (MSCs) expressing progerin showed significantly increased levels of downstream effectors in the NOTCH signalling pathway (Scaffidi and Misteli, 2008). Coupling the epigenetic changes with gene expression will further elucidate the key factors that are misregulated by progerin in HGPS disease progression.

Defective cellular differentiation

The expressions of A-type lamins are developmentally regulated, suggesting a potential role of A-type lamins in controlling development and differentiation. Indeed, defects in tissue differentiation have been reported in a number of laminopathies. HGPS patients mainly exhibit differentiation defects in mesenchymal lineages. Consistently, *in vitro* study demonstrated that induced expression of progerin in MSCs (hMCSs) leads to enhanced differentiation towards osteocytes and to reduced differentiation into adipocytes. Further expression analysis suggested that high levels of NOTCH, an essential regulator of stem cell differentiation, are responsible for the differentiation misregulation in progerin-expressing hMCSs (Scaffidi and Misteli, 2008).

The retinoblastoma transcriptional regulator (RB) is essential for cell cycle control and differentiation of mesenchymal lineages. As a key regulator, hypophosphorylated RB acts as a pocket protein that binds and inhibits E2F family transcriptional factors, thereby pausing in the G1 cell cycle phase. This RB-mediated checkpoint allows for execution of cellular differentiation. Once cyclin/cyclin-dependent kinase (CDK) complexes phosphorylate RB, RB releases E2Fs, which drive the cell into the S-phase of the cell cycle. Lamins A and C bind RB and these interactions appear to be essential for preventing the destruction of RB by proteosomes (Johnson *et al*., 2004). It is likely that the presence of progerin disrupts the lamin A/C-RB complex and RB becomes less stable in HGPS cells. Besides the overall RB protein stability, two recent studies proposed alternative explanations of the misregulation of the RB signalling axis in HGPS. One study reported that there is a significant reduction in the levels of hyperphosphorylated RB in HGPS, with overall RB mRNA and protein levels remaining unchanged (Dechat *et al*., 2007). In contrast, a recent gene expression analysis showed transcriptional suppression of the RB regulatory axis in fibroblast cells from five HGPS patients (Marji *et al*., 2010).

The exploration of differentiation defects in patients has been extremely challenging due to the rarity and early mortality of HGPS. Researchers gathered information using patient-derived skin fibroblasts, established cell lines to overexpress lamin A or progerin, and used mouse models that recapitulate some, but not all, of the symptoms of HGPS (Zhang *et al*., 2011). Excitingly, the revolutionary technique of reprogramming fully differentiated cells into induced pluripotent stem cells (iPSCs) has provided a new model to explore the pathogenesis of HGPS (Zhang *et al*., 2011; Liu *et al*., 2011). HGPS–iPSCs show an absence of progerin or lamin A and have normal nuclear membrane and chromatin organisation. Furthermore, HGPS–iPSCs were able to be differentiated into neural progenitors,

endothelial cells, fibroblasts, vascular smooth muscle cells (VSMCs) and MSCs. Characterisation of these differentiated cells revealed that the MSCs, VSMCs and fibroblasts accumulated the highest levels of progerin, DNA damage and nuclear abnormalities (Zhang *et al*., 2011). These studies also uncovered additional downstream targets of progerin, DNA-dependent protein kinase catalytic subunit (DNAPKCs) and its regulatory subunits Ku70/Ku80. The DNAPKC holoenzyme, whose expression is downregulated in HGPS primary fibroblasts, regulates proliferation, telomere length and genomic stability in somatic cells (Liu *et al*., 2011). Levels of DNAPKCs were restored in HGPS-derived iPSCs only to be lost on differentiation. Thus, the downregulation of this regulatory element in differentiated cells was dependent on the presence and accumulation of progerin.

Treatment of HGPS

As a result of successful collaborations between researchers, clinicians and the families of HGPS patients, the pace of advance from gene discovery to drug therapy for children with HGPS is unprecedented.

Farnesyltransferase inhibitors (FTIs), a class of cancer drugs, were first considered as a potential treatment option based on the observation that permanently farnesylated prelamin A was the cause of a progeria-like phenotype in Zmpste24$^{-/-}$ mice (Fong *et al*., 2004). Shortly after that, other groups reported that FTI treatment of primary HGPS fibroblasts (or complementary systems) efficiently reverses the disease-related abnormal nuclear shape through mislocalising progerin away from the nuclear periphery (Capell *et al*., 2005; Glynn and Glover, 2005; Toth *et al*., 2005). Studies in mouse models of progeria demonstrated that FTIs could ameliorate the severity of disease symptoms and prevent the onset and delay progression of cardiovascular disease (Fong *et al*., 2006; Capell *et al*., 2008). In 2007, 28 HGPS children participated in a clinical trial of an FTI (lonafarnib), which concluded in December 2009 (http://www.progeriaresearch.org/clinical_trial.html).

FTI-treated cells compensate for farnesyltransferase inhibition by prenylation of prelamin A by geranylgeranyltransferases (Capell and Collins, 2006). This mechanism could be inhibited by the addition of statins and aminobisphosphonates to the drug cocktail. Treatment of Zmpste24$^{-/-}$ mice with this cocktail of three drugs inhibited both farnesylation and geranylgeranylation of progerin and prelamin A, and consequently, dramatically improved the aging-like phenotypes and extended lifespan (Varela *et al*., 2008). In late 2009, a total of 45 HGPS patients started a clinical trial with three drugs: Pravastatin (a stain drug typically used to treat cardiovascular disease), Zoledronic acid (a bisphosphonate used to help prevent bone damage in cancer patients) and Lonafarnib (http://www.progeriaresearch.org/clinical_trial.html).

FTI treatment has recently been shown to cause a centrosome separation defect during mitosis, leading to the formation of donut-shaped nuclei in normal and HGPS cells (Verstraeten *et al*., 2011). These donut-shaped nuclei exhibit defects in karyokinesis and cause cells to proliferate slowly. Such changes may explain some of the anticancer effects of these drugs but may also provide impetus for continued research.

A recent publication identified rapamycin, an immunosuppressant drug, as another potential therapeutic treatment. Rapamycin, which is widely used to prevent organ transplantation rejection, can prolong the life of adult mice (Anisimov *et al*., 2010). In progeria fibroblasts, rapamycin treatment normalised the nuclear morphology, delayed the onset of cellular senescence, and enhanced progerin clearance through autophagic mechanisms (Cao *et al*., 2011a). These encouraging results have attracted much attention and may stimulate further analysis of the use of rapamycin as a therapy for HGPS. Additional avenues of treatment may be directed against the alternative splice donor site in exon 11 of *LMNA*. Specifically, Osorio *et al*. described a mouse strain carrying an HGPS mutation in the *Lmna* gene (*Lmna*^{G609G}; 1827C > T; Gly609Gly), and progerin is produced via genetic mechanisms (abnormal splicing) identical to those observed in HGPS children. This mouse recapitulated many cellular and clinical manifestations of HGPS such as accumulation of progerin, transcriptional alterations, premature aging and cardiovascular abnormalities. Using antisense morpholinos that efficiently block the pathogenic splicing of prelamin A mRNA, researchers were able to significantly improve the progeriod symptoms and dramatically increase their lifespan (Osorio *et al*., 2011). Together, these advances have opened the doors for new treatment options that can not only alleviate symptoms, but may also one day eliminate the cause, the mutant lamin A progerin.

Connections with Normal Aging

Research into the cellular basis of laminopathies has yielded exciting results and led to the potential therapeutics to treat these devastating diseases. Moreover, several recent publications have convincingly linked progerin production with normal aging. A number of studies determined that progerin is present in small amounts in cells from normal individuals, suggesting that the aberrant splicing event leading to progerin expression may play a role in normal physiological aging (Scaffidi and Misteli, 2006; Cao *et al*., 2007; Olive *et al*., 2010; Cao *et al*., 2011b). Concordantly, cardiovascular pathology of HGPS patients mirrors that of geriatric patients and vascular progerin production in normal patients increases significantly over time (Olive *et al*., 2010). The relationship between HGPS and normal aging was further elucidated by a study by Cao *et al*. which showed that progressive telomere shortening during cellular senescence activates progerin production and leads to

alternative splicing of several other genes (Cao *et al*., 2011b).

Conclusion

Studies on the cellular pathology of laminopathies have considerably advanced our understanding of the function and structure of the nuclear lamins. In addition, these drastic diseases provide us with unique experimental models that can be used to examine normal aging processes. Finally, treatment options for patients are expanding as scientists constantly seek new ways to mitigate disease symptoms, and to find more targeted interventions to these diseases, including through reducing or even eliminating the production of mutant forms of lamins.

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