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REVIEW

Mouse models of laminopathies

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Abstract

The A- and B-type lamins are nuclear intermediate filament proteins in eukaryotic cells with a broad range of functions, including the organization of nuclear architecture and interaction with proteins in many cellular functions. Over 180 disease-causing mutations, termed 'laminopathies,' have been mapped throughout *LMNA*, the gene for A-type lamins in humans. Laminopathies can range from muscular dystrophies, cardiomyopathy, to Hutchinson–Gilford progeria syndrome. A number of mouse lines carrying some of the same mutations as those resulting in human diseases have been established. These *LMNA*-related mouse models have provided valuable insights into the functions of lamin A biogenesis and the roles of individual A-type lamins during tissue development. This review groups these *LMNA*-related mouse models into three categories: null mutants, point mutants, and progeroid mutants. We compare their phenotypes and discuss their potential implications in laminopathies and aging.

Key words: aging; farnesylation; lamin A; laminopathies; progeria.

Introduction

The nuclear lamina is made of polymers of evolutionarily highly conserved type V intermediate filament (IF) proteins called lamins (Dechat *et al.*, 2008). In vertebrates, there are two types of lamin proteins, A- and B-type lamins. B-type lamins have an acidic isoelectric point and remain associated with membranes during mitosis. A-type lamins have a neutral isoelectric point and are fully solubilized during mitosis (Stuurman *et al.*, 1998). A small amount of the various lamin isoforms are also present in the nucleoplasm (Dechat *et al.*, 2010): Nucleoplasmic B-type lamins appear to be relatively static, while A-type lamins are highly mobile. It is unclear how exactly lamins assemble in the nucleus of somatic cells and whether or not they co-polymerize *in vivo* (Gruenbaum *et al.*, 2005; Dechat *et al.*, 2010).

Four A-type lamins arise from *LMNA* in mammals: lamin A, lamin C, lamin AΔ10, and lamin C2. Lamins A and C are the two main protein products of *LMNA* (Capell & Collins, 2006) (Fig. 1A). Unlike ubiquitously expressed B-type lamins, A-type lamins are expressed in a tissue-specific manner only during or after differentiation, with increasing expression levels after terminal differentiation and growth arrest (Stuurman *et al.*, 1998). Lamins A and C are produced in equivalent amounts with the exception of the central nervous system where only Lamin C is produced due to a brain-specific miRNA to the 3′ untranslated region of lamin A mRNA (Jung *et al.*, 2012).

A-type lamins begin as prelamins with Ras-like C-terminal-CAAX motifs, where C is cysteine, A is an aliphatic amino acid, and X is variable. The CAAX box triggers an ordered process of post-translational modifications, in which every step depends on the previous modification (Worman *et al.*, 2009; Dechat *et al.*, 2010) (Fig. 1). Modification begins with farnesylation of the cysteine residue by a farnesyltransferase (Dechat *et al.*, 2010). The AAX is then removed by the zinc metalloproteinase Zmpste24/FACE1 (Dechat *et al.*, 2010). The carboxy-terminal cysteine is then carboxymethylated by isoprenylcysteine carboxyl methyltransferase (Icmt) (Dechat *et al.*, 2010). Following these steps, an additional 15 amino acids are removed from the carboxyl terminus of prelamin A by Zmpste24/FACE1, which is abolished in Hutchinson–Gilford progeria syndrome (HGPS) (Vorburger *et al.*, 1989; Dechat *et al.*, 2010) (Fig. 1B). Lamin C is produced by an alternative splice site in exon 10 and does not have a CAAX box, so it is not modified (Dechat *et al.*, 2010) (Fig. 1A).

With many different proteins binding to lamins directly or indirectly, mutations in *LMNA, LMNB1*, and *LMNB2* have shown a myriad of tissue-specific effects (Capell and Collins, 2006; Tsai *et al.*, 2006). Over 180 mutations have been mapped throughout *LMNA* alone. These mutations have been associated with at least 14 diseases, termed 'laminopathies', including autosomal forms of Emery–Dreifuss muscular dystrophy (AD-EDMD), dilated cardiomyopathy (DCM), and HGPS. To understand how mutations in *LMNA* result in different diseases, mouse models carrying some of the mutations found in humans with laminopathies have been created. In this review, we group the lamin A-related mouse models into three categories: null mutants, point mutants, and progeroid mutants, and discuss their implications with focuses on recent developments.

Null mutants

$Lmna^{-/-}$ and $Lmna^{GT-/-}$

The first lamin A mutant mouse model created was lamin A and C null ($Lmna^{-/-}$) (Table 1). These mice showed numerous defects, including reduced stores of white fat, growth retardation, cardiac arrhythmia, and abnormal emerin targeting (Sullivan *et al.*, 1999). In addition, a recent study by Kubben *et al.* developed a novel $Lmna^{GT-/-}$ mouse model, whose *Lmna* gene was disrupted by a reporter gene (Kubben *et al.*, 2011). The reporter showed *Lmna* promoter to be activated as soon as day 11 during embryonic development in organs including heart, liver, and somites. With the loss of A-type lamins, these organs and tissues showed defective differentiation and maturation during the postnatal stage. These mice generally die before they are weaned. Consistent with the Kubben $Lmna^{GT-/-}$ mouse model, in human, a homozygous *LMNA* nonsense mutation has been reported in a newborn patient, which resulted in a complete absence of lamin A and C and had a lethal phenotype at birth (van Engelen *et al.*, 2005).

Significant molecular insights have been revealed by the *Lmna* null mouse model. *Tong el al.* showed that lack of lamin A/C could reduce

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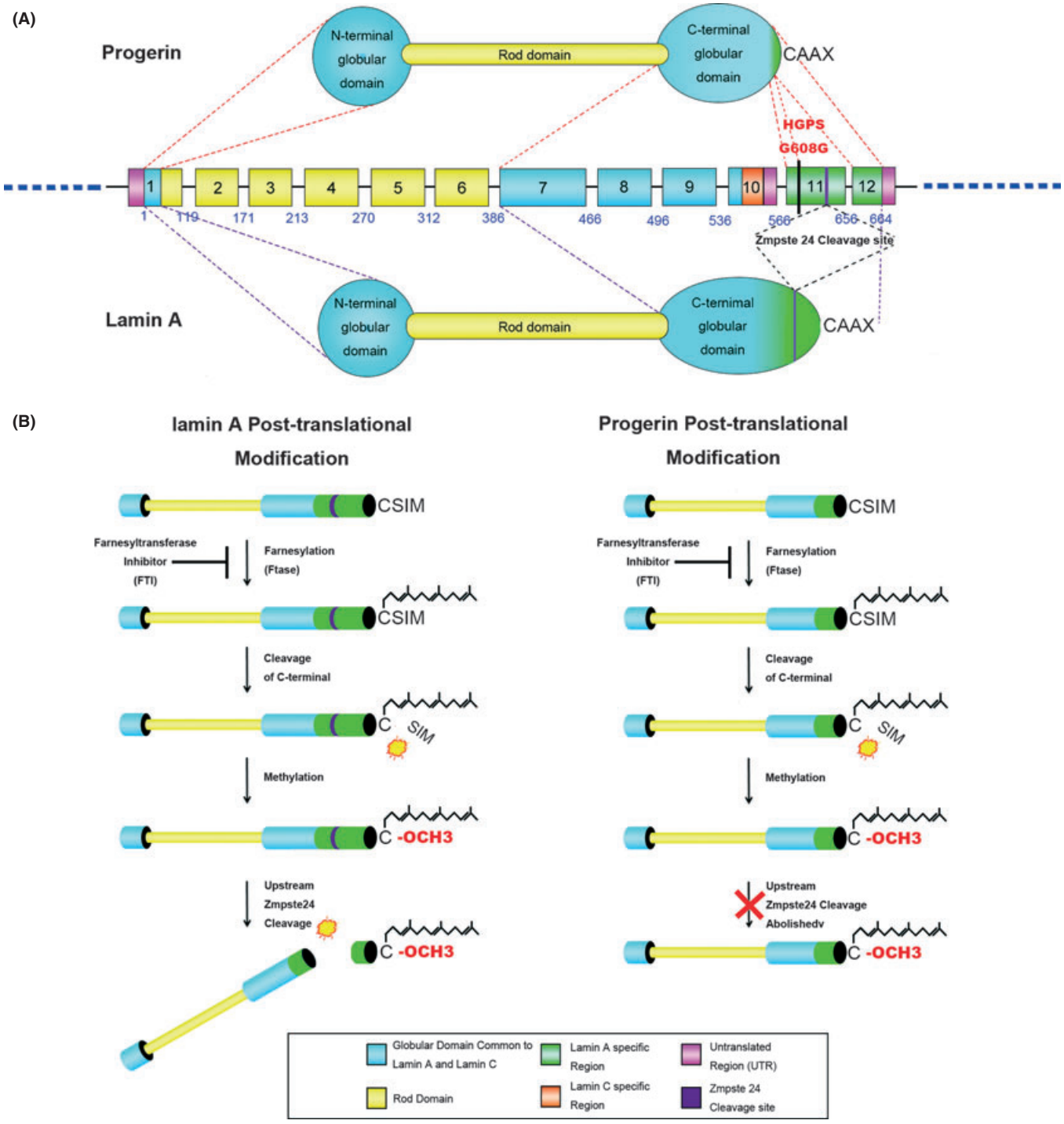

Fig. 1 (A) Structure of lamin A and Progerin. The LMNA gene (not to scale) is made up of 12 exons, encoding two globular domains and a central α-helical coiled-coil rod domain. Lamin C is encoded by exons 1 to 9 and a portion of exon 10. Lamin A adds exons 11 and 12 and removes the lamin C-specific region. Progerin results from the activation of a cryptic splicing site by the mutation, which leads to an internal deletion of 50 amino acids in exon 11. Progerin lacks the Zmpste24 cleavage site and thereby retains the Cterminal tail in its mature form. (B) Post-translational processing of lamin A and Progerin. Translation of the LMNA gene yields the prelamin A protein, which has the amino acids CSIM at the C-terminus. After farnesylation, a modification step that can be blocked by farnesyltransferase inhibitors (FTIs), the terminal three amino acids (SIM) are cleaved by the ZMPSTE24 endoprotease, and the terminal farnesylated cysteine undergoes carboxymethylation. A second cleavage step by the ZMPSTE24 endoprotease then removes the terminal 15 amino acids, including the farnesyl group. This final cleavage step is blocked in progerin.

both muscle bone strength through increasing fat infiltration by 2.5- to 4- folds and 40-folds, respectively (Tong *et al.*, 2011). Concomitantly, increased PPAPγ and CEBP/α (pro-adipogenesis factors) as well as decreased Wnt-10b/β-catenin levels were observed, arguing that Lamin A/C might influence both myogenesis and osteogenesis by regulating adipogenesis (Tong *et al.*, 2011). Additionally, lamin A/C might also regulate the osteogenic transcription factor Runx2 through down-regulating its co-localizing protein MAN-1 (Li *et al.*, 2011). These results

provide new insights into the possible mechanisms underlying muscle, bone, and adipose tissue abnormalities related to lamin A/C deficiency. Potential treatment options for lamin A/C deficiency have also been explored using *Lmna*$^{-/-}$ mice. In a very recent study, *Ramos et al.* showed that mTORC1 (mammalian target of rapamycin complex 1) signaling pathway was up-regulated in cardiac and skeleton muscle tissues in *Lmna*$^{-/-}$ mice (Ramos *et al.*, 2012). Treating the mutant mice with rapamycin, an mTOR inhibitor, was able to reverse the elevated mTORC1 signaling, rescue cardiac and skeleton muscle function, and elongate lifespan (Ramos *et al.*, 2012).

Lamin A only (LAO), Prelamin A only (PLAO), and Lamin C only (LCO)

The discovery of a link between prelamin A processing and progeroid disorders has led to investigations of the physiological importance of lamin A biogenesis (Capell *et al.*, 2005; Capell & Collins, 2006). Coffinier *et al.* reasoned that prelamin A processing might be essential, given its conservation throughout vertebrate evolution. To test the importance of prelamin A processing, they generated lamin A-only mice (LAO) by deleting intron 10 (eliminating lamin C synthesis) and DNA sequences between the last codon of lamin A and the prelamin A stop codon (bypassing processing). Prelamin A-only (PLAO) mice were created by the deletion of intron 10 only (Coffinier *et al.*, 2010). Thus, in *Lmna*$^{LAO/LAO}$ animals, lamin A was synthesized directly; but in *Lmna*$^{PLAO/PLAO}$, it was generated through prelamin A processing. Despite eliminating the prelamin A processing steps, the steady-state levels of mature lamin A in both mutant lines were comparable. On the whole-animal level, *Lmna*$^{LAO/LAO}$ mice appeared to be fertile and healthy for more than 2 years. However, *Lmna*$^{LAO/LAO}$ and *Lmna*$^{PLAO/PLAO}$ fibroblasts showed a higher frequency of nuclear blebbing than *Lmna*$^{+/+}$ fibroblasts, which implies that cellular abnormalities do not necessarily correlate to the severity of tissue pathologies. In addition, there were increased amounts of mature lamin A in the nucleoplasm of *Lmna*$^{LAO/LAO}$ fibroblasts, implying a potential role of prelamin A processing in nuclear lamina targeting (Coffinier *et al.*, 2010).

Coffinier et al. also implies that lamin C is dispensable in mouse tissues when the mature lamin A is present. Conversely, mice producing only lamin C (LCO) but no lamin A also appeared to be perfectly normal on a whole-animal level (Fong *et al.*, 2006b). Together, it appears that neither lamin A nor lamin C is required in mouse, but the complete absence of all A-type lamins is lethal. Similarly, disruptions of B-type lamins in mouse resulted in striking phenotypic changes in bone and lung, defects during organogenesis, and premature death at birth (Vergnes *et al.*, 2004; Kim *et al.*, 2011). It has been proposed that a balanced ratio of A- to B-type lamins is essential for maintaining normal nuclear architecture and tissue homeostasis (Hutchison, 2012).

Point mutants

H222P and N195K

Two mouse lines carried missense mutations in *LMNA* gene have been reported: one histidine to proline substitution at amino acid 222 (H222P), which causes AD-EDMD in humans, and an asparagine to lysine substitution at amino acid 195 (N195K), which causes DCM-CD1 in humans (Arimura *et al.*, 2005; Mounkes *et al.*, 2005) (Table 2). Both of the homozygous mutant lines showed phenotypes mimicking the corresponding diseases in the human situation, with Lmna$^{H222P/H222P}$ developing

Table 1 Null mutants

Abbreviation	Mutation	Disease in humans caused by mutation	Homozygous mouse phenotype	Heterozygous mouse phenotype	Literature
Lmna$^{-/-}$	Exon 8 to middle of exon 11 deleted	Limb-girdle muscular dystrophy	Normal at birth, followed by reduction in growth rate. Muscular dystrophy and weakening of cardiac muscle. Resembles Emery–Dreifuss muscular dystrophy (EDMD). Death by 8 weeks of age.	No apparent abnormalities.	Sullivan, T. D. J. Cell Biol. (1999); van Engelen, B.G.M. Neurology (2005)
LmnaGT$^{-/-}$	A promoter trap construct was inserted into LMNA intron 2 resulting in a LMNA- pgeo fusion allele	N/A	LMNA promoter is activated at day E11 during embryonic development. Growth retardation at 2 weeks, impaired postnatal hypotrophy with cardiac myocytes, skeleton muscle hypotrophy, decreased subcutaneous adipose tissue, decreased adipogenic differentiation, and metabolic derangements.	No apparent abnormalities.	Kubben, N. Nucleus (2011)
Lamin C Only (LCO)	Last 150 nucleotides of exon 11 and all of intron 11 deleted	None	No apparent abnormalities.	No apparent abnormalities.	Fong, L.G. J. Clin. Invest. (2006)
Lamin A Only (LAO)	Intron 10, last 30 nucleotides of exon 11, intron 11, and first 24 nucleotides of exon 12 deleted	N/A	No apparent abnormalities.	Not described.	Coffinier, C. J. Biol. Chem. (2010)
Prelamin A Only (PLAO)	Intron 10 deleted, but exons 11 and 12 left unaffected	N/A	No apparent abnormalities.	Not described.	Coffinier, C. J. Biol. Chem. (2010)

Table 2 Point Mutants

Abbreviation	Mutation	Disease in humans caused by mutation	Homozygous mouse phenotype	Heterozygous mouse phenotype	Literature
N195K	N195K missense mutation on exon 3	Dilated cardiomyopathy with conduction system disease (DCM-CD1)	Slight growth retardation, enlarged and weakened heart (dilated cardiomyopathy), increased fibrosis of heart, and conduction system defects. Appeared outwardly normal until shortly before death at average age of 12 weeks.	Heterozygous mice lived as long as wild-type siblings.	Mounkes, L.C. Hum. Mol. Genet. (2005)
H222P	H222P missense mutation on exon 4	Autosomal dominant Emery–Dreifuss muscular dystrophy (AD-EDMD)	Growth retardation, hunched position, stiff walking posture, and rapid shallow breathing. Increased fibrosis of heart, muscular dystrophy, and dilated cardiomyopathy. Earlier onset at adulthood and more severe phenotype for men, with death by 9 months. Women died by 13 months.	No apparent abnormalities.	Arimura, T. Hum. Mol. Genet. (2005)
M371K	Mini-gene construct carrying a missense mutation M371K, under the control of heart selective a myosin heavy chain promoter	Autosomal dominant Emery–Dreifuss muscular dystrophy (AD-EDMD)	N/A	Significantly lower birth rate, shorten lifespan (2–7 weeks), increased eosinophilia, and fragmentation of cardiomyofibrils, nuclear pyknosis, and edema. Multifocal lesions without fibrosis or significant inflammation.	Wang, Y. Hum. Mol. Genet. (2006)
L530P	L530P missense mutation yielding at least two differently spliced forms of both lamin A and lamin C: (1) skipping of exon 9 (2) inclusion of complete exon 9 and part of intron 9 with an in-frame stop codon	Autosomal dominant Emery–Dreifuss muscular dystrophy (AD-EDMD)	Similar to HGPS in humans, mice showed growth retardation, underdevelopment, and degeneration of cardiac muscle, an undersized jaw, abnormal dentition, a loss of subcutaneous fat, and decreased hair follicle density. Death by 4 weeks.	No apparent abnormalities.	Mounkes, L.C. Nature (2003b); Hernandez, L. Dev. Cell. (2010)

dystrophic condition in skeletal and cardiac muscles and Lmna$^{N195K/N195K}$ showing premature death of severe arrhythmia (Stewart *et al.*, 2007).

M371K

Although homozygous H222P and N195K mutants faithfully recapitulated human disease, heterozygous mice showed no apparent abnormalities. This is in contrast to the human situation in which EDMD is caused largely through autosomal dominant lamin A mutations. To determine whether lamin A mutations can cause diseases in a dominant manner in mouse, Wang *et al.* generated a transgenic mouse overexpressing human *LMNA* gene carrying a methionine to lysine substitution at amino acid 371(M371K), which causes AD-EDMD in human. This transgene is under the control of a heart-sensitive α-myosin heavy chain promoter that directs expression only in heart (Wang *et al.*, 2006).

Heterozygous M371K mice showed a significantly lower birth rate than expected, likely due to the detrimental effects of the mutant protein during early embryo development. Born mutants usually can survive 2–7 weeks after birth and showed increased eosinophilia and fragmentation of cardiomyofibrils, nuclear pyknosis, and edema. The lesions were multifocal and without fibrosis or significant inflammation, indicating acute or sub-acute injury. However, the phenotypes in this model did not fully mimic the situations in human EDMD, which is more gradual and dilated. This discrepancy may be caused by the high expression of M371K mutant protein in this model (Wang *et al.*, 2006).

L530P

In another effort to create a mouse model for AD-EDMD, Mounkes and colleagues introduced a nucleotide base substitution of proline for leucine at residue 530 (L530P) in the mouse *Lmna* gene (Mounkes *et al.*, 2003b; Hernandez *et al.*, 2010). This mouse model should be interpreted with caution, because L530P mutation yielded at least two different splicing forms for both lamin A and lamin C in the transgenic animals: a major form with internal deletion of exon 9 and a minor form with an inclusion of complete exon 9 and part of intron 9 with an in-frame stop codon. Homozygous L530P mice exhibited phenotypes somewhat similar to those observed in HGPS patients, including growth retardation, thinning and extensive apoptosis in the vascular smooth muscle cell (VSMC) layer of the pulmonary artery, reduced bone density, and increased bone fragility. *Lmna*$^{L530P/L530P}$ postnatal fibroblasts (MAFs) showed accelerated senescence and death. Interestingly, gene expression analysis revealed significant changes in the expression of extracellular matrix (ECM) genes in L530P MAFs. When grown on an ECM deposited by wild-type cells, proliferative failure of *Lmna*$^{L530P/L530P}$ MAFs was rescued. Hernandez *et al.* postulated that L530P might disrupt nuclear pore function, thereby interfering with import and export of β-catenin and reducing nuclear Lef1 levels as a consequence. A reduction in Lef1 then would result in reduced bone mass and growth retardation via reduced transcription of ECM genes. In addition, Hernandez *et al.* propose that HGPS could be a disease of the ECM and connective tissue and suggest that this may open new routes for intervention and treatment (Hernandez *et al.*, 2010).

Progeroid mutants

HG

HGPS is the one of the most severe forms of laminopathies (Table 3). To create a mouse model that produces large amounts of progerin, Yang and colleagues generated a knock-in mutant *Lmna* allele, *Lmna*^{HG} (HG stands for HGPS) that exclusively produces progerin. This allele was created by the deletion of intron 10, intron 11, and the last 150 nucleotides of exon 11, and thus, the sole product from this allele was the mutant protein progerin (Mounkes *et al.*, 2003a; Yang *et al.*, 2005; Varga *et al.*, 2006; Hernandez *et al.*, 2010). Both homozygous and heterozygous HG mice all showed phenotypes similar to children with HGPS, including a loss of subcutaneous fat, alopecia, osteoporosis, and premature death (Mounkes et al., 2003a; Yang *et al.*, 2005; Varga *et al.*, 2006; Yang *et al.*, 2006; Hernandez *et al.*, 2010). However, no cardiovascular defects were reported in this model (Mounkes et al., 2003a; Yang *et al.*, 2005; Varga *et al.*, 2006; Hernandez *et al.*, 2010).

G608G BAC

The second HGPS mouse model, created by Dr. Collins' group in 2006, carries the G608G mutated human *LMNA* on a 164-kb bacterial artificial chromosome (BAC). Unlike the HG model, this G608G BAC transgenic model contains the human *LMNA* gene and substantial flanking DNA to include regulatory signals for expression and splicing. The G608G BAC transgenic mice did not show the external characteristics of progeria, but very interestingly, they developed progressive loss of VSMC, a feature observed in the autopsies of some HGPS patients (Varga *et al.*, 2006). It is unclear why the phenotype of this model essentially limited to VSMC. The authors proposed that progerin-expressing VSMCs are in particularly vulnerable locations due to the shear forces by blood, and other tissues might show phenotypes if the mice lived longer or produced more progerin (Varga *et al.*, 2006).

Zmpste24$^{-/-}$

Zmpste24 is the enzyme that carries the function of processing the farnesylated prelamin A in mouse and human (Capell & Collins, 2006). In humans, the loss of *Zmpste24* results in a condition known as restrictive dermopathy, which causes perinatal death (Capell & Collins, 2006). Two Zmpste24 deficient models (*Zmpste24*$^{-/-}$) were generated in 2002 (Bergo *et al.*, 2002; Pendas *et al.*, 2002). In both *Zmpste24*$^{-/-}$ models, no mature lamin A was produced, and farnesylated prelamin A accumulated as a consequence of Zmpste24 deficiency. In the model developed by Bergo *et al.*, the exon 8 that encodes the zinc-binding domain was replaced with a neomycin resistance cassette. The homozygous null mice are normal at birth and later develop abnormalities including growth retardation, alopecia, muscle weakness, and most notably multiple spontaneous bone fractures (Bergo *et al.*, 2002). In the second Zmpste24 null model designed by Pendas *et al.*, Zmpste24 sequence was interrupted after codon 39. This homozygous null animal displayed growth retardation, dilated cardiomyopathy, muscular dystrophy, lipodystrophy, and premature death (Pendas *et al.*, 2002).

The phenotypes in both *Zmpste24*$^{-/-}$ models mimic those in HGPS patients, suggesting the accumulation of farnesylated A-type lamins at least partially contribute to HGPS phenotypes. In support of this notion, a number of studies in cell cultures and animal models with HGPS (*HG, G608G BAC*, and *Zmpste24*$^{-/-}$) demonstrated that blocking farnesylation of progerin or prelamin A with farnesyltransferase inhibitors (FTIs) could alleviate progeriod phenotypes (Capell et al., 2005; Yang *et al.*, 2005; Fong *et al.*, 2006a; Yang *et al.*, 2006; Capell *et al.*, 2008). In addition, Davies *et al.* created a knock-in mouse model that carries a nonfarnesylated prelamin A and reported that these animals developed a dilated cardiomyopathy but had no phenotypes of progeria (Davies *et al.*, 2010). While this study alerts the potential side effect of developing cardiomy-

Table 3 Progeria Mutants

Abbreviation	Mutation	Disease in humans caused by mutation	Homozygous mouse phenotype	Heterozygous mouse phenotype	Literature
HG	Intron 10, intron 11, and last 150 nucleotides of exon 11 deleted	HGPS	A loss of subcutaneous fat, alopecia, osteoporosis, and growth retardation. Death by 4 weeks.	A loss of subcutaneous fat, alopecia, growth retardation, and bone disease.	Yang, S.H. Proc. Natl. Acad. Sci. USA (2005); Yang, S. H. J. Clin. Invest. (2006)
G608G BAC	164-kb human BAC containing LMNA with G608G mutation	HGPS	N/A	No external phenotype, but progressive loss of vascular smooth muscle cells (VSMC). Arterial calcification and extracellular matrix deposition in older mice. No consistent differences in mortality between wild-type mice and transgenic mice.	Varga, R. Proc. Natl. Acad. Sci. USA (2006)
tetop_LA^{G608G}	Full coding region of human LA^{G608G} (exon 1-11, intron 11, and exon 12) ligated to tetop vector, IRES, and eGFP. Tetop-LA^{G608G} mice intercrossed with K5tTA transgenic mice	HGPS	N/A	After induction, growth retardation, dental abnormalities and numerous skin abnormalities. Premature death at 7 weeks for postnatal day 0 mice and 14 weeks for postnatal day 21 mice.	Sagelius, H. J. Cell Sci. (2008)
Keratin14-progerin	Minigene construct encoding human progerin under the control of a keratin 14 promoter	HGPS	N/A	Abnormal nuclear shape of primary keratinocytes. Normal hair growth and wound healing.	Wang, Y. Hum. Mol. Genet. (2008)
Zmpste24$^{-/-}$	Exon 8 replaced with a neomycin resistance casette	Restrictive Dermopathy and HGPS	Severe growth retardation, reduced bone density with spontaneous fractures, muscle weakness, kyphosis, hair loss, micrognathy, and dental abnormalities. Death at 6-7 months of age.	Normal for the first 12 months. Growth retardation, muscle weakness, and hair loss show by 15 months of age.	Bergo, O.M. Proc. Natl. Acad. Sci. USA (2002)
Zmpste24-/-	Exon 2 and 3 replaced by a promoter-less IRES p-geo, which contains a splice acceptor sequence. Zmpste 24 sequence interrupted after codon 39	Restrictive Dermopathy and HGPS	Growth retardation and premature death. Dilated cardiomyopathy, muscular dystrophy, and lipodystrophy.	Morphologically indistinguishable from wild-type littermates.	Pendas, A.M. Nat. Genet. (2002)
nHG	Intron 10, intron 11, and last 150 nucleotides of exon 11 deleted. Point mutation in exon 12 changed cysteine in CaaX motif to serine	N/A	Reduced subcutaneous fat and weight. Progressive rib fractures with increasing age. Death by 17 weeks.	Better growth, more body fat, and reduced rib fractures compared with HG/+. Death by 36 weeks.	Yang, S. H. J. Clin. Invest. (2008)
csmHG	Intron 10, intron 11, and last 150 nucleotides of exon 11 deleted. Three nucleotides of exon 12 specifying isoleucine in CaaX motif deleted	N/A	Slight thinning of the left ventricular wall at 12 months.	No apparent abnormalities.	Yang, S. H. Hum. Mol. Genet. (2011)
Lmna^{G609G}	Point mutation in Lmna gene (c.1827C>T;p. G609G)	HGPS	Growth rate reduction after 3 weeks, progressive loss of weight, infertility, abnormal posture, and marked curvature of spine. Death at the age of around 100 days.	A similar premature aging phenotypes as observed in homozygous mice show after 8 months. Death occured at an average of 242 days.	Osorio, F.G. Sci Transl. Med. (2011)

opathy in the long-term FTI treatments, this study further support that the farnesylation is central to disease phenotype in HGPS.

nHG and csmHG

Besides the retention of farnesylation, progerin has an internal 50 amino acid deletion near the C terminus (Fig. 1). Yang *et al.* cited fears that nonfarnesylated progerin may retain the ability to elicit disease (Yang *et al.*, 2008). To investigate this possibility, mice expressing a nonfarnesylated version of progerin were generated. The new mutant allele ($Lmna^{nHG}$) was identical to the original $Lmna^{HG}$ allele, except the cysteine of the CAAX motif was replaced with a serine (CSIM→SSIM). Significantly, homozygous and heterozygous nHG mice showed a similar but less severe version of the phenotypes than those observed in HG mice. Likewise, the percentage of misshapen nuclei was lower in nHG MEFs than in HG MEFs. As expected, FTIs had no effect on nHG MEFs. These results suggest that nonfarnesylated progerin is still toxic, and blocking farnesylation by FTIs may not fully reverse the progerin-induced phenotypes in HGPS patients. In addition, the authors found that progerin levels were lower in nHG MEFs and tissues than in HG MEFs, suggesting that the lack of farnesylation might reduce steady-state levels of the protein. The reduced levels of progerin in nHG could explain why the phenotypes are less severe than those in HG mice. The authors cautiously acknowledge that it is possible that nonfarnesylated progerin created from a cysteine-to-serine substitution could itself be toxic (Yang *et al.*, 2008).

To examine whether cysteine-to-serine substitution is toxic in nHG model, Yang *et al.* applied an alternative strategy for producing nonfarnesylated progerin by deleting the isoleucine in the CAAX motif to create a protein ending in CSM, rather than SSIM (Yang *et al.*, 2011). Progerin levels were similar in csmHG and nHG mice. Like wild-type lamin A, most of the nonfarnesylated progerin in csmHG and nHG mouse was located at the nuclear rim. In contrast to the phenotypes in nHG mice, csmHG mice showed normal bone density, adipose tissue, weight, and survival, all of which were indistinguishable from wild-type littermate controls. The only noticeable defect in homozygous csmHG mice is a slight reduction in left ventricular posterior wall thickness, which did not result in sudden death. These new findings on csmHG model suggest that cysteine-to-serine substitution in nHG model is likely to be toxic. One alternative explanation for the discrepancy between nHG and csmHG models is that progerin's 50-amino acid deletion may be toxic and that the deletion of the C-terminal isoleucine may neutralize the toxicity of protein (Yang *et al.*, 2011).

tetop-LA^{G608G}

To avoid potential toxicity of progerin during early development and examine the effect of progerin on epidermal keratinocytes, Sagelius *et al.* constructed an inducible system that expresses human lamin A and progerin under the control of a tet-operon (Sagelius *et al.*, 2008a; Sagelius *et al.*, 2008b). The minigenes, which included exons 1–11, intron 11, and exon 12, expressed either wild-type lamin A or the HGPS G608G mutant (tetop-LA^{wt} and tetop-LA^{G608G}, respectively). Expression was targeted to keratin 5-expressing tissues by intercrossing tetop-LA^{wt} and tetop-LA^{G608G} transgenic mice with transgenic mice expressing K5tTA (Diamond *et al.*, 2000), which directs the expression of minigenes to the basal cells of the interfollicular epidermis and hair follicles. In these bi-transgenic animals expressing progerin, a loss of subcutaneous fat, fibrosis of the dermis, and incomplete development of sebaceous glands characterized the final phenotypes. Other notable abnormalities were dental problems, hair thinning, growth retardation, and premature death. It was speculated that dental abnormalities were a partial cause of growth retardation and premature death, so mice were fed a softer diet of dissolved pellets on the cage floor, which increased survival from 7 to 29 weeks (Sagelius et al., 2008a; Sagelius *et al.*, 2008b). Interestingly, the bi-transgenic animals expressing wild-type human lamin A used as controls did not show weight loss or premature death, but demonstrated a phenotype of partial hair loss with regions of skin crusting. Further examination showed an accumulation of prelamin A in the control line, possibly caused by high levels of expression.

A follow-up study with this mouse model by the same group showed decreased stem cell population in the epidermal tissues and impaired wound healing ability. In line with this, isolated primary keratinocytes were characterized with reduced proliferation potential and colony forming ability, which might be due to reduced p63 level and increased DNA damage. Furthermore, multiple inflammatory factors were elevated in the keratinocytes of the mutant mice, leading to senescence associated secretion phenotype. These data support the idea that impaired adult stem cell regeneration ability as a cause of HGPS premature phenotype (Rosengardten *et al.*, 2011).

Keratin 14-progerin

As the skin is severely affected in HGPS patients, another effort has been made by Wang and colleagues to examine the effects of progerin on skin. They created a transgenic mouse model that expresses human progerin in epidermal tissues under the control of a keratin-14 promoter (keratin 14-progerin) (Wang *et al.*, 2008). Keratin-14 promoter gives a similar tissue-selective expression of progerin as the keratin 5 promoter used by Sagelius *et al.* However, although the primary keratinocytes isolated from keratin 14-progerin mice showed abnormal nuclear shape, these animals had normal hair and wound healing, even after intercrossing to $Lmna^{-/-}$ mice to eliminate endogenous wild-type lamin A. Again, these observations lead to the question of the association of cellular phenotypes with tissue pathologies. As proposed by Varga *et al.*, certain tissues, such as striated muscle, in which cells are continuously subjected to mechanical stress, maybe more sensitive to nuclear structural abnormalities, while other tissues, such as epidermis, may be able to function despite some changes in the nuclear shape (Wang *et al.*, 2008).

Lmna^{G609G}

Recently, *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 abnormal splicing identical to those observed in HGPS children (Osorio *et al.*, 2011). $Lmna^{G609G/G609G}$ mice were born normal until 3 weeks after birth with subsequent reduction in growth rate, progressive loss of weight, infertility, abnormal posture, marked curvature of spine, and died prematurely at the age of 100 days on average. Heterozygous mice also died prematurely, but at a reduced rate: most exhibited a normal phenotype until 8 months after birth and died at an average age of 242 days. On a cellular level, nuclear abnormalities were found as progerin accumulated. Cardiovascular abnormalities were also found in the mutant mice, which may relate to the premature death of the mutant mice. Moreover, the mutant mice also displayed aberrant hormone concentrations, manifesting in hypoglycemia and abnormal reduction in the levels of insulin-like growth factor. Morpholino antisense oligonucleotides reduced progerin expression in the $Lmna^{G609G/+}$ fibroblasts to undetectable levels. The correction of nuclear abnormalities appeared to accompany reduction in progerin expression. *In vivo* studies with morpholinos showed significant

improvements in body weight, reduced lordokyphosis, and extended lifespan for *Lmna*$^{G609G/G609G}$ mutant mice, suggesting a new approach of gene therapy for HGPS (Osorio *et al.*, 2011).

Together, these *LMNA*-related mouse models have provided valuable insights into the functions of lamin A biogenesis and the roles of individual A-type lamins during tissue development. Moreover, these mouse models also provided useful *in vivo* systems for treatment testing.

Lamin A and aging

Studies on lamin-related mouse models have led to valuable discoveries about the pathogenesis of and possible treatments for laminopathies. Rapamycin and its derivative everolimus work to reverse the aging effects in HGPS cells through activated clearance of mutant proteins (Cao *et al*., 2011b; Driscoll *et al.*, 2012). Future study will be required to examine the effects of rapamycin in various lamin-related mouse models.

The usefulness of the lamin A-related mouse models may also extend to research on the normal aging process. Since 2006, accumulating evidence has to some extent bridged the gap between HGPS and the physiological aging process. Fibroblast samples from elderly wild-type individuals have been shown to have a variety of common features with those from HGPS patients, including aberrant nuclear morphology, increased γH2AX foci number, down-regulation of heterochromatin protein expression, and altered histone modification patterns (Goldman *et al*., 2004; Scaffidi & Misteli, 2005). In addition, the appearance of progerin in fibroblasts and skin samples from healthy individuals further suggests that progerin may play a role in normal aging (Scaffidi and Misteli, 2006; McClintock *et al.*, 2007). Moreover, in a 2007 study on the mechanism of progeria pathogenesis, *Cao et al.* found that progerin forms insoluble cytoplasmic or membrane-bound aggregates that cause chromosomal lag during mitosis in both HGPS cells and normal cells(Cao *et al.*, 2007).

Cardiovascular disease is a leading cause of death for HGPS patients. Interestingly, there are many similarities between the cardiovascular pathology of HGPS patients and that of normal elderly individuals (Olive *et al.*, 2010). For instance, progerin was detected in coronary arteries in non-HGPS individuals. Interestingly, recent work demonstrated that accumulation of prelamin A was detected in aged VSMCs, suggesting prelamin A as a novel biomarker of VSMC aging (Ragnauth *et al.*, 2010). In addition, Bökenkamp *et al.* reported that activation of *LMNA* cryptic splicing is involved in vascular remodeling in the circulatory system during normal closure of the neonatal ductus arteriosus, implying a novel role of progerin in normal development (Bokenkamp *et al.*, 2011).

These findings, together with recent evidence that progerin can cause cellular senescence in normal fibroblasts through dysfunctional telomeres (Cao *et al.*, 2011a), have generated new and profound insight into the normal aging process. They also lend unprecedented value and meaning to progerin-related mouse models. Looking ahead, studies on these mouse models may not only help to explore novel treatments for patients with laminopathies, but also further upgrade one's knowledge on the normal aging process.

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