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Review

Lamin A/C, laminopathies and premature ageing

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Summary. Lamin A/C belongs to type V intermediate filaments and constitutes the nuclear lamina and nuclear matrix, where a variety of nuclear activities occur. Lamin A/C protein is firstly synthesized as a precursor and is further proteolytically processed by the zinc metallo-proteinase Ste24 (Zmpste24). Lamin A/C mutations cause a series of human diseases, collectively called laminopathies, the most severe of which is Hutchinson Gilford progeria syndrome (HGPS) and restrictive dermopathy (RD) which arises due to an unsuccessful maturation of prelamin A. Although the exact underlying molecular mechanisms are still poorly understood, genomic instability, defective nuclear mechanics and mechanotransduction, have been hypothesized to be responsible for laminopathy-based premature ageing. Removal of unprocessed prelamin A (progerin) or rescue of defective DNA repair could be potential therapeutic strategies for the treatment of HGPS in future.

Key words: Lamin A/C, Laminopathy, Premature ageing

Introduction

HGPS is a rare genetic disorder that is characterized by an early onset premature ageing and is predominantly caused by a G608G mutation in the *LMNA* gene. The lamin A/C protein belongs to type V intermediate filaments and constitutes the nuclear lamina and nuclear matrix. It is firstly synthesized as a precursor, which is further proteolytically processed by Zmpste24. The G608G mutation activates a cryptic splicing site in exon 11 and causes a 50-amino-acid truncation that includes the second proteolytic site of Zmpste24, resulting in a truncated unprocessed prelamin A, termed progerin. Mice harboring $Lmna^{L530P/L530P}$ mutation or deficient for prelamin A processing enzyme – Zmpste24 recapitulate many progerial features found in HGPS, including short stature, hair loss, cardiomyopathy, lipodystrophy and muscular atrophy etc. Nonsense mutations in ZMPSTE24 are associated with RD, a severe form of progeria. Although aberrant lamin A leads to premature ageing in both human and mouse, the exact molecular mechanism remains unclear.

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Lamins and *LMNA* gene

Lamins belong to type V intermediate filaments and are the major components of nuclear lamina underneath the inner nuclear membrane (INM). In vertebrates, lamins are classified into two groups according to their behavior during mitosis: A-type lamins which dissociate from the nuclear membrane, and B-type lamins which remain associated with the nuclear membrane (Moir et al., 2000). A growing number of investigations have shown that A-type lamins are only expressed in differentiated cells and are not essential for cell viability; in contrast, B-type lamins are ubiquitously expressed in most cells, and are essential for cell viability (Harborth et al., 2001). The fundamental roles of lamins are further emphasized by developmental studies using transgenic techniques. Lamin A/C knockouts are born indistinguishable from wild-type littermates and can survive for 4 to 8 weeks, suggesting that A-type lamins are not essential for murine development (Sullivan et al., 1999). On the other hand, lamin B_1 deficiency causes embryonic lethality (Vergnes et al., 2004). A-type lamins consist of four proteins – lamin A, lamin $A_{\Delta 10}$, lamin C and C_2, which are alternatively spliced from the *LMNA* gene located on chromosome 1q21.2-q21.3 in human (Wydner et al., 1996). Three B-type lamins are encoded by two separate genes, *LMNB1* for lamin B_1 and *LMNB2* for lamin B_2 and B_3. Of those, either lamin B_1 or B_2 is expressed in all cells, while lamin B_3 is only found to be expressed in spermatocytes (Stuurman et al., 1998). The *LMNA* gene contains 12 exons with two polyadenylation signals (ATTAAA for lamin C/C_2 and AATCAA for lamin $A/A_{\Delta 10}$) located on exon 10 and exon 12, respectively (Lin and Worman, 1993). Lamin A and C share the first 566 amino acids. Lamin A has a specific

98-amino-acid carboxyl tail and lamin C has a unique 6-amino-acid carboxyl tail (Fig. 1). There is increasing evidence showing that lamin A/C is only expressed in cells that start to differentiate, including adult stem cells (Constantinescu et al., 2006). Lamin $A_{\Delta 10}$ is expressed in several tumor cell lines and some normal tissues (Machiels et al., 1996), and lamin C_2 is reported to be specifically expressed in germline, where no other A-type lamins are found (Hutchison, 2002).

The lamin A protein is firstly synthesized as a presursor with a conserved CAAX (Cysteine-Aliphatic-Aliphatic-any Amino Acid, Cys-Ser-Ile-Met in prelamin A) motif in the carboxyl tail (Fig. 2). Maturation of prelamin A is a sophisticated process, involving farnesylation (Beck et al., 1990), endoproteolysis (Pendas et al., 2002) and methylation (Bergo et al., 2002). More precisely, the CAAX motif is firstly recognized by farnesyltransferase (FT), which catalyzes the addition of a farnesyl isoprenoid (15 carbons) to the cysteine residue. Then, ZMPSTE24, also known as farnesylated-proteins converting enzyme 1 (FACE-1), cleaves behind farnesylcysteine to release -AAX (Corrigan, 2005). This is followed by methylation on the same cysteine by isoprenylcysteine methyltransferase (ICMT). Finally, ZMPSTE24 or other unidentified enzymes catalyze a second proteolytic cleavage to remove an additional 15 amino acids on the C-terminus. The mature lamin A is approximately 2 kDa less than prelamin A (Agarwal et al., 2003; Corrigan et al., 2005). The mature lamin A protein is comprised of a 28-residue positively charged globular head domain, a central a-helical rod-like domain containing four coiled-coil repeats (coil 1A, 1B, 2A and 2B) that are separated by three evolutionary conserved linker regions, referred to as L1, L12 and L2, a conserved nuclear localization signal (NLS), and one Ig-like structure domain formed by 116 residues on the C-terminus (Fig. 3). The coiled-coil domains are thought to mediate the dimerization of lamin A/C proteins (Broers et al., 2006) and the Ig-like domain is thought to regulate interaction between lamin A/C and DNA, protein and lipid (Goldman et al., 2005).

During evolution, the complexity of lamin proteins are gradually increased (Cohen et al., 2001). Although nuclear pore complex (NPC) is conserved in yeast *Saccharomyces cerevisiae* (Rout et al., 2000), no lamins or other associated INM proteins have been identified so far. Lamins and the INM proteins seem to be unique in multicellular systems (Erber et al., 1998). In vertebrates, two types and a total of seven lamins (A, C, $A_{\Delta 10}$, C_2, B_1, B_2 and B_3) are encoded from three different genes (*Lmna*, *Lmnb1* and *Lmnb2*). In *Drosophila melanogaster*, one A-type (lamin C) and one B-type lamin (lamin Dm_0) have been identified. In *Caenorhabditis elegans*, only one B-type lamin (Ce-lamin) was found (Stuurman et al., 1998). The increasing complexity of lamins seems to be correlated with the increase in the efficiency of nuclear envelope disassembly during mitosis (Cohen et al., 2001). Among all lamins, evolutionarily, B-type lamins are more conserved; among A-type lamins, lamin C is more conserved than lamin A, which undergoes complicated post-translational modifications to become mature (Fig. 4). Recently, it was shown that lamin C-only mice were phenotypically the same as wild-type animals, indicating the dispensable role of the lamin A protein (Fong et al., 2006b). These observations have raised several interesting questions. What is the evolutional role of lamin A? Why does lamin A need such complicated

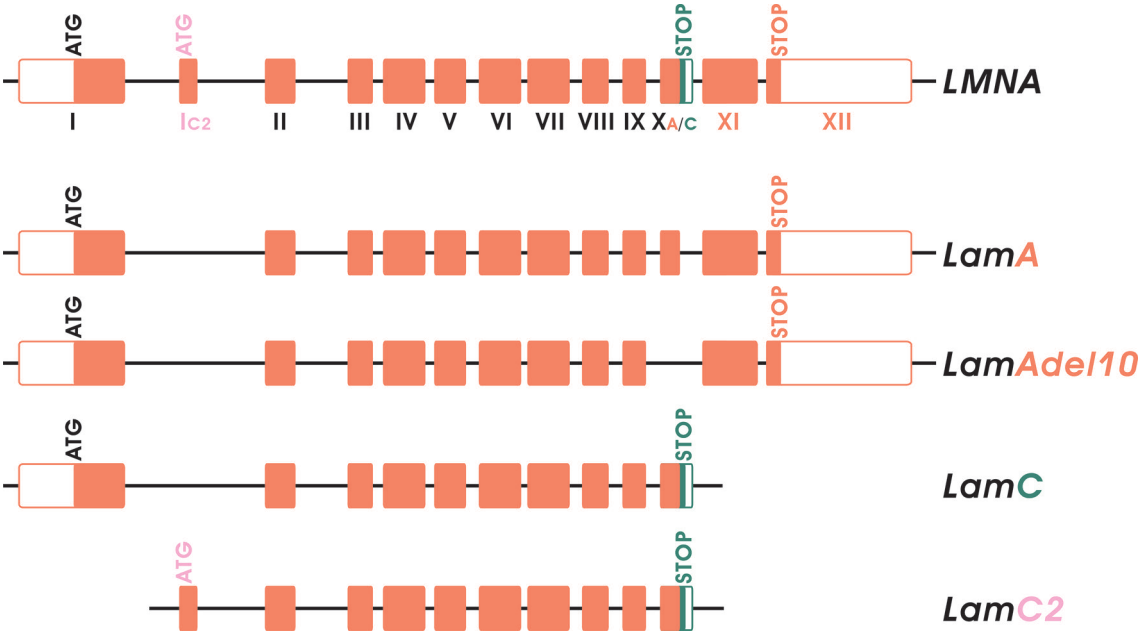

Fig. 1. *LMNA* and A-type lamins. The *LMNA* gene has 12 exons and contains two polyadenylation signals, which are located in exon 10 and 12, and are utilized by lamin C/C_2 and lamin A/$A_{\Delta 10}$ respectively. As a consequence of alternative splicing, the first exon in lamin C_2 is different from other A-type lamins, and lamin $A_{\Delta 10}$ shares identical exons with lamin A but lacks exon 10.

post-translational modifications, the deficiency of which usually results in accelerated ageing syndromes? Can lamin A also functionally compensate for the loss of lamin C?

Although the exact mechanism is yet to be elucidated, in mammals, the lamina assembly of A-type lamins is most likely dependent on their polymerization and pre-existing B-type lamins on lamina (Hutchison, 2002). Similar to A-type lamins, B-type lamins also undergo post-translational -AAX processing (CAIM in human lamin B_1 and CYVM in human lamin B_2), including farnesylation by FT, endoproteolysis by RCE-1, and methylation by ICMT, which results in a farnesylated and methylated Cysteine tail. In *Rce-1*$^{-/-}$ or *Icmt*$^{-/-}$ MEFs, B-type lamins aggregate in the nucleoplasm (Maske et al., 2003), suggesting that nuclear lamina association of B-type lamins depends on the methyl, alone, or together with the farnesyl group on the C-terminus. In agreement with this is the observation that inhibition of farnesylation by FT inhibitors (FTIs) in mammalian cells also disrupted nuclear lamina association of both B-type and A-type lamins (Maske et al., 2003). However, neither mature lamin A nor lamin C has farnesyl or methyl groups in the carboxyl tail, indicating different pathways of nuclear lamina association. The observation of unaffected lamina assembly of B-type lamins in *Lmna*$^{-/-}$ MEFs (Sullivan et al., 1999) suggested an A-type lamin-independent manner. On the other hand, an *in vitro* experiment using *Xenopus* egg extracts showed that recombinant lamin A protein can be assembled into lamina filaments only in the presence of lamin B_3 (Dyer et al., 1999), indicating a B-type lamin-dependent incorporation of A-type lamins onto the filamentous nuclear lamina. Observations that reassembly of A-type lamina only occurred after successful B-type lamina reassembly during mitosis in cultured cells (Moir et al., 2000) and nucleoplasmic aggregation of endogenous lamin A/C in Hela cells transfected with mutated lamin B_1 (Dechat et al., 2000) also argue strongly in favor of B-type lamin-dependent assembly of A-type lamina. Although a recent study suggested that A-type lamina is not affected in *Lmnb1*$^{-/-}$ cells (Malhas et al., 2007), it is still possible that unaffected lamin B_2 in *Lmnb1*$^{-/-}$ cells might have a compensatory role in guiding A-type lamins to the filamentous meshwork of nuclear lamina. Further

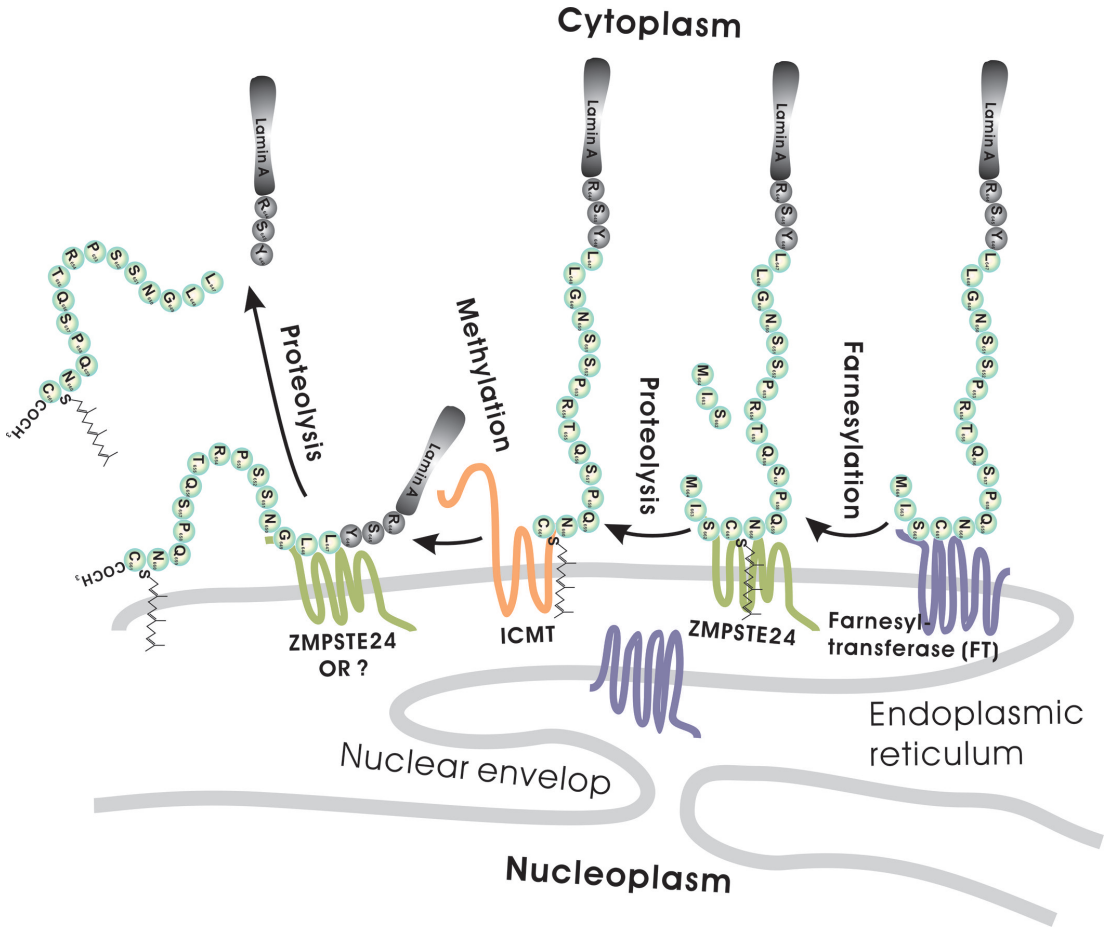

Fig. 2. Post-translational processing of prelamin A. Lamin A is firstly synthesized as a precursor with conserved CAAX motif on the C-terminus. Its maturation requires mainly four steps. Firstly, the cysteine residue of CAAX is farnesylated by farnesyl transferase (FT) located on the endoplasmic reticulum (ER). Secondly, Zmpste24 mediates a proteolytic cleavage after farnesyl-cysteine to release the last three amino acids (AAX). Then the exposed farnesyl-cysteine is further methylated by ICMT. Finally, Zmpste24 (or other unidentified enzyme?) mediates the second proteolytic cleavage to remove an additional 15 amino acids. Mature lamin A is 18-amino-acid shorter than prelamin A and does not contain any farnesyl or methyl group on the C-terminus.

detailed studies on the distribution of lamin A/C in lamin B_1 and B_2 double knockout cells will shed light on this issue.

Lamin A and C also show different assembly properties. In tumor cell lines that lack lamin A or in *Lmna*$^{-/-}$ MEF cells, endogenous or ectopically expressed lamin C aggregated in the nucleoplasm, which can be restored by introduction of lamin A (Vaughan et al.,

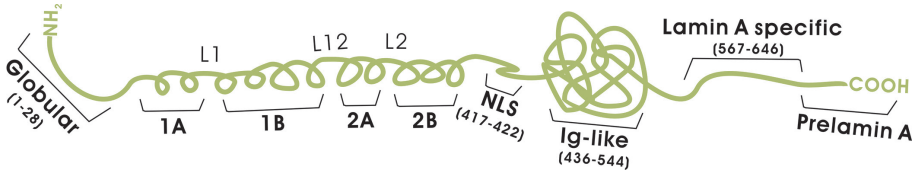

Fig. 3. Schematic structure of lamin A/C. Prelamin A is composed of a 28-residue positively charged N-terminal globular domain, a central α-helical rod-like domain containing four coiled-coil repeats (coil 1A, 1B, 2A and 2B) that are separated by three evolutionary conserved linker regions, referred to as L1, L12 and L2, a conserved nuclear localization signal (NLS), one Ig-like structure formed by approximately 116 residues on the C-terminus and a positively charged C-terminal globular domain, where prelamin A has a unique 98-residue tail, and lamin C has a specific 6-amino-acid peptide. The last 18 amino acids are removed by endoproteolysis, which can be catalysed by Zmpste24.

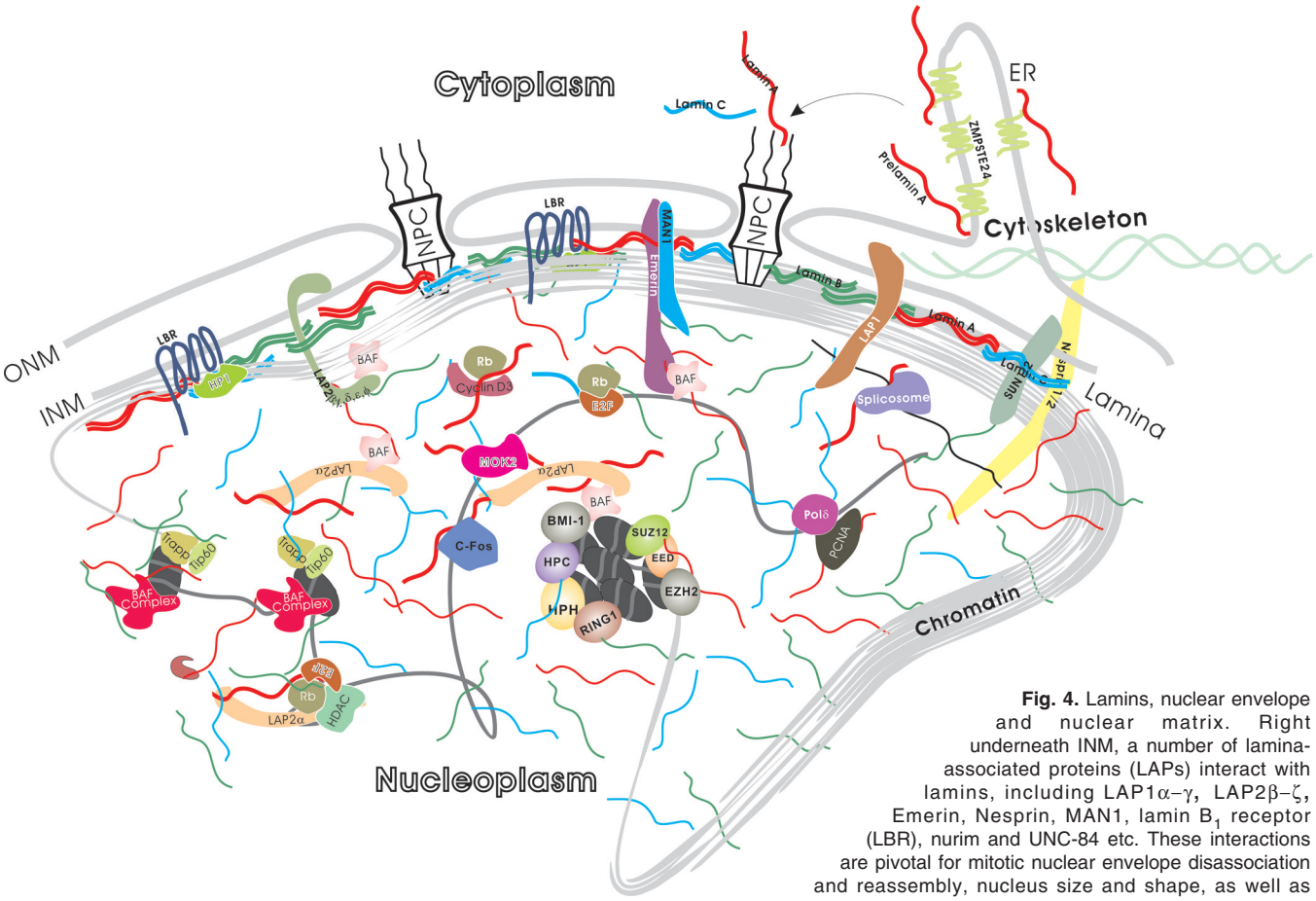

Fig. 4. Lamins, nuclear envelope and nuclear matrix. Right underneath INM, a number of lamina-associated proteins (LAPs) interact with lamins, including LAP1α–γ, LAP2β–ζ, Emerin, Nesprin, MAN1, lamin B_1 receptor (LBR), nurim and UNC-84 etc. These interactions are pivotal for mitotic nuclear envelope disassociation and reassembly, nucleus size and shape, as well as correct positioning and spacing of NPCs. Lamin A/C also interacts with DNA directly though the C-terminal tail or through lamina-associated proteins, such as LAP1 and LAP2β or nucleoplasmic LAP2α, and this association guides nuclear peripheral positioning and keeps constitutive silencing of heterochromatin. Recently, the interaction between LAP2α and lamin A was demonstrated to be capable of promoting proliferation of human fibroblasts. Among these INM associated or nucleoplasmic interacting partners, a special group containing LEM domains can directly interact with BAF, suggesting a potential role of lamin A/C in the regulation of chromatin modification or remodeling. Lamin A/C interacts with transcription factors, including Rb, SREBP1, MOK2 and c-Fos, to regulate their activities. Lamin A/C is also involved in mRNA splicing via the interaction with SC-35. Recently, lamin A/C was reported to be co-precipitated with Mel-18, heterogeneous nuclear ribonucleoprotein E1 (hnRNP E1), ubiquitin conjugating enzyme E2I (UBC9), EGF1 and cyclin D3, indicating its diverse functions.

2001), indicating that nuclear lamina assembly of lamin C depends on lamin A. When microinjected into Swiss 3T3 cells, lamin A can incorporate into nuclear lamina more rapidly than lamin C, and co-microinjection of lamin A and lamin C can facilitate the incorporation of lamin C but not lamin A. These results again indicate the lamin A-dependent manner of lamin C-lamina assembly (Pugh et al., 1997).

Based on these and other observations not reviewed here, we and others (Hutchison, 2002) proposed a "homodimerization" model of nuclear lamina assembly. The B-type lamins in the nucleoplasm firstly form parallel homodimers (B_1B_1 or B_2B_2) and subsequently tetramers in a "head-tail" manner ($B_1B_1B_1B_1$ or $B_2B_2B_2B_2$) mediated by Rod-like coiled-coil domains. The tetramers are then tethered to INM by interaction with lamin B receptor (LBR) or other pre-existing INM associated proteins through the methyl or farnesyl/methyl moiety (Ye and Worman, 1994). A-type lamins are also assembled into homodimers in the same manner as B type (AA and CC), followed by the formation of homotetramers (AAAA or CCCC) or heterotetramers (AACC), and finally bind to B-type lamins to form the filamentous meshwork or nuclear lamina underneath INM.

Recently, Navarro et al. (2006) proposed a "lateral diffusion" model of nuclear lamina assembly. Prelamin A and prelamin B_1/B_2 share similar post-translational modification of farnesylation, proteolysis and methylation. The farnesyl group introduced by FT mediates the anchorage of prelamin A and prelamin B_1/B_2 to the cytosolic leaflet of ER to facilitate the following proteolytic cleavage by ZMPSTE24 or RCE-1 and methylation via IMCT. After the first three steps of post-translational processing, prelamin B_1/B_2 remains on ER through the retained farnesyl group and translocates to INM by lateral diffusion. In contrast, the intermediate prelamin A is further processed by ZMPSTE24 to remove a 15-residue peptide containing the farnesyl/methyl Cysteine on the C-terminus. Then, the mature lamin A is released from ER, locates to the nucleoplasm through NPC-mediated transportation and binds to pre-existing B-type lamins on INM to form nuclear lamina, or remains in the nucleoplasm to regulate other nuclear activities.

A-type lamins not only exist in the nuclear lamina, but are also distributed throughout the nuclear interior and are associated with different nuclear bodies. Although it is still unclear whether the nucleoplasmic portions are in the same configuration as those on the lamina, the functional importance of A-type lamins in diverse nuclear activities has been continuously emphasized by a growing number of interacting partners in the nuclear lamina, as well as the nucleoplasm. Right underneath INM, a number of lamina-associated proteins (LAPs) were shown to interact with lamins, including LAP1α-γ, LAP2ß-ζ (Foisner and Gerace, 1993), Emerin (mutations identified in X-linked EDMD) (Lee et al., 2001), Nesprin (Mislow et al., 2002a,b), MAN1, lamin B_1 receptor (LBR), nurim, and UNC-84 (Cohen et al., 2001). These interactions are pivotal for mitotic nuclear envelope disassociation and reassembly, nucleus size and shape, as well as correct positioning and spacing of NPCs, which mediate transportations between the nucleoplasm and cytoplasm (Cohen et al., 2001). Lamin A/C also interacts with DNA directly through the carboxyl-terminal tail (Stierle et al., 2003) or through lamina-associated proteins, such as LAP1 and LAP2ß or nucleoplasmic LAP2α, and this association is proved to be important for nuclear peripheral positioning and constitutive silencing of heterochromatin (Cohen et al., 2001). Recently, the interaction between LAP2α and lamin A was demonstrated to promote the proliferation of human fibroblasts (Pekovic et al., 2007). Among these INM associated or nucleoplasmic interacting partners, a special group containing LEM (LAP2, Emerin, MAN1) domain can directly interact with barrier to autointegration factor (BAF) (Furukawa, 1999).

Lamin A/C can also directly interact and regulate activity of transcription factors, including retinoblastoma protein (Rb), sterol response element binding protein 1 (SREBP1), MOK2 (Dreuillet et al., 2002) and c-Fos (Ivorra et al., 2006). Rb is a tumor suppressor and a negative cell cycle regulator. Wild-type Rb protein contains 928 amino acids with one large N-terminal domain and three C-terminal pocket domains (A-C). While the N-terminal domain mainly mediates oligomerization, pocket A and B interact with E2F and D-type cyclins to negatively regulate cell cycle progression by masking E2F transactivation domain (Cao et al., 1992; Dowdy et al., 1993; Ewen et al., 1993). The pocket C domain was found to be associated with c-Abl tyrosine kinase (Welch and Wang, 1993, 1995), MDM2 (Xiao et al., 1995), A-type lamins (residues 247-355) and LAP2α (Ozaki et al., 1994; Markiewicz et al., 2002). Rb pocket domains are also associated with histone deacetylase, HDAC1, to regulate cell cycle progression though deacetylation of histones in E2F-regulated promoters of specific cell cycle proteins (such as cyclin E), which can be reversed by administration of histone deacetylase inhibitor, trichostatin A (TSA) (Brehm et al., 1998; Luo et al., 1998; Magnaghi-Jaulin et al., 1998). Recent studies revealed that lamin A/C-LAP2α-Rb complex was crucial for promoting sub-nuclear localization of Rb and preventing it from proteasomal degradation (Johnson et al., 2004). In *Lmna*$^{-/-}$ cells, Rb was targeted for degradation and protein level was dramatically reduced. *Lmna*$^{-/-}$ MEF cells also shared similar growth and division characteristics with *Rb*$^{-/-}$ cells (Johnson et al., 2004). The mis-localization and degradation of Rb in *Lmna*$^{-/-}$ cells compromised the differentiation capacity of muscular satellite cells, with dysregulated essential differentiation factors, such as decreased MyoD, desmin, and M-cadherin, and increased Myf5 (Frock et al., 2006). Moreover forced expression of MyoD or desmin can restore the differentiation potential in *Lmna*$^{-/-}$ myoblasts

(Frock et al., 2006).

Lamin A/C also plays essential roles in RNA splicing. Using a nucleoplasmic lamin A/C specific monoclonal antibody, LA-2H10, which only stained speckles in interphase nuclei without labeling the nuclear rim, lamin A/C was reported to co-localize with RNA splicosome, indicating its potential role in mediating RNA metabolism (Kumaran et al., 2002).

Lamin A/C has also been shown to interact with polycomb group protein Mel-18, heterogeneous nuclear ribonucleoprotein E1 (hnRNP E1), ubiquitin conjugating enzyme E2I (UBC9), and EGF1, suggesting a potential role of A-type lamins in chromatin modification, RNA metabolism and ubiquitylation-mediated protein degradation, as well as signaling pathways (Zhong et al., 2005). More recently, Mariappan et al. (2007) reported another lamin A/C interacting protein, cyclin D3, indicating a pivotal role of lamin A/C in regulating cell cycle progression. A novel nucleoplasmic protein, lamin companion 1 (Lco1), was also reported to colocalize and interact with A-type lamins in the nuclear interior (Vlcek et al., 2004).

Sterol response element binding protein 1 (SREBP1) is an adipocyte differentiation factor, which specifically binds to the carboxyl-terminal tail of prelamin A, but not mature lamin A or lamin C. Recent studies have linked familial partial lipodystrophy (FPLD) to mutations in lamin A/C and peroxisome proliferator-activated receptor (PPARγ), which is normally activated by SREBP1. Lamin A/C mutations in FPLD mainly concentrate on the C-terminus and usually lead to prelamin A accumulation in the nuclear rim. Prelamin A sequesters and inhibits SREBP1, which subsequently down-regulates PPARγ activity. The accumulation of unprocessed prelamin A is also thought to be the molecular mechanism underlying the anomalous distribution of body fat in premature ageing syndromes caused by mutated lamin A/C (Capanni et al., 2005).

Narf, although its exact function is not clear yet, is another reported protein that specifically interacts with prenylated prelamin A (Barton and Worman, 1999). This interaction most likely mediates nuclear envelope association or post-translational modification of prelamin A, including proteolysis and methylation (Corrigan, 2005).

Zinc metalloproteinase STE24 (ZMPSTE24)

ZMPSTE24, human ortholog of yeast *Saccharomyces cerevisiae* Ste24p, is a zinc metalloproteinase located on the endoplasmic reticulum (ER) and nuclear envelope. In yeast, Ste24p is responsible for maturation of mating pheromone α-factor (Fujimura-Kamada et al., 1997; Tam et al., 1998). Recent studies demonstrated that, during murine development, the expression of Zmpste24 was observed as early as E10.5 in all tested tissues, with the highest level in heart and kidney (Pendas et al., 2002). Although the mammalian ortholog of α-factor, still not yet identified, was speculated as the potential substrate, nuclear protein prelamin A is so far the only reported substrate of ZMPSTE24 in human and mouse (Pendas et al., 2002). This implication is further strengthened by the crossing between *Zmpste24*$^{-/-}$ to *Lmna*$^{-/-}$ mice. The *Lmna*$^{-/-}$*Zmpste24*$^{-/-}$ compound mutants were phenotypically indistinguishable from *Lmna*$^{-/-}$ mice, indicating that prelamin A might be the only substrate of Zmpste24 in mouse (Fong et al., 2004; Varela et al., 2005).

Laminopathies

In 1986, Fisher and Chaudhary et al. for the first time identified the cDNA encoding lamin A/C proteins. The first four *LMNA* mutations were reported almost 13 years later in patients with autosomal dominant Emery-Dreifuss muscular dystrophy (EDMD2; OMIM 181350) (Bonne et al., 1999). Since then, the essential role of lamin A/C has been continuously highlighted by large body of investigations. To date, more than 237 different *LMNA* mutations, which lead to at least 163 protein variants, are known to be related to at least 10 degenerative disorders (http://www.umd.be:2000) and are collectively referred to as primary laminopathies (Fig. 5 summarizes most of the common mutations related to non-progeroid laminopathies and Fig. 6 summarizes all mutations reported so far to be linked to progeroid laminopathies). When different affected tissues are taken into account, laminopathies can be re-divided into four classes, those with affected striated muscles; peripheral nerves; adipose tissues; and those suffering from premature ageing with multiple tissue degeneration.

Laminopathies with striated muscular atrophy

To date, lamin A/C mutations that cause striated muscular dystrophy account for around 60% of laminopathies (Burke and Stewart, 2006), including EDMD2, autosomal dominant limb girdle muscular dystrophy 1B (LGMD1B; OMIM 159001) and dilated cardiomyopathy, 1A (DCM1A; OMIM 115200). EDMD is a rare skeletal muscle disorder with cardiac conduction defects, where approximately 50% are diagnosed to be caused by mutations of EMD, the gene encoding emerin, in an X-linked manner, or by mutations of lamin A/C protein in an autosomal dominant or recessive way (Bonne et al., 1999, 2000; Felice et al., 2000; Raffaele Di Barletta et al., 2000; Helbling-Leclerc et al., 2002; Ben Yaou et al., 2005). Lamin A/C mutations also cause autosomal dominant DCM1A (Fatkin et al., 1999; Brodsky et al., 2000; Genschel et al., 2000b; Speckman et al., 2000), with muscular dystrophy in a cardiac-specific manner, without affecting skeletal muscle and LGMD1B (Muchir et al., 2000), characterized by proximal muscle weakness and wasting. In strong agreement with these clinical presentations of EDMD2, LGMD1B and DCM1A, the

same *LMNA* mutation can lead to any of these three syndromes in different affected family members, which might be attributable to various genetic modifications and/or environmental influences (Brodsky et al., 2000; Vytopil et al., 2002).

Laminopathies affecting peripheral nerves

Homozygous lamin A/C missense mutation R298C is the first and only *LMNA* mutation, associated with Charcot Marie tooth disease type 2B1 (CMT2B1; OMIM 605588). It is characterized by slightly reduced or unaffected nerve conduction velocities and motor neuron demyelination and axonal degeneration (De Sandre-Giovannoli et al., 2002).

Laminopathies with loss or reduced adipose tissues

Familial partial lipodystrophy, Dunnigan type (FPLD2; OMIM 151660), is inherited in an autosomal dominant manner. Patients with FPLD2 have uneven fat distribution after the onset of puberty, loss of subcutaneous white adipose tissue from limbs, gluteal, and truncal regions, with simultaneous accumulation of white adipose tissue in the neck, face and abdominal areas. Three substitutions on Arg482 residue (R482W, R482Q and R482L) of lamin A/C are found to be responsible for the majority of FPLD2 (Cao and Hegele, 2000; Genschel et al., 2000a; Shackleton et al., 2000; Speckman et al., 2000; Vigouroux and Capeau, 2005). In addition to these, are these five different mutations of G465D, K486N, R582H, R584H and V440M (Hegele et al., 2000). Interestingly, *LMNA* mutations related to FPLD2 are usually located on the surface of the Ig-like domain, while the mutated residues associated with striated muscular dystrophies in the same region usually reside inside the Ig-like domain (Krimm et al., 2002).

Congenital generalized lipodystrophy, type 2 (CGL2, OMIM 269700), also known as Seip syndrome, was found to be related with dominant point mutation T10I of lamin A/C (Csoka et al., 2004). CGL2 is characterized by lipoatrophy from birth and severe insulin resistance associated with hyperpigmentation of the skin, muscular hypertrophy, hepatomegaly, glucose intolerance or diabetes, and hypertriglyceridemia.

Progeria

HGPS (OMIM 176670) is an extremely rare genetic disorder of early onset premature ageing, also referred to

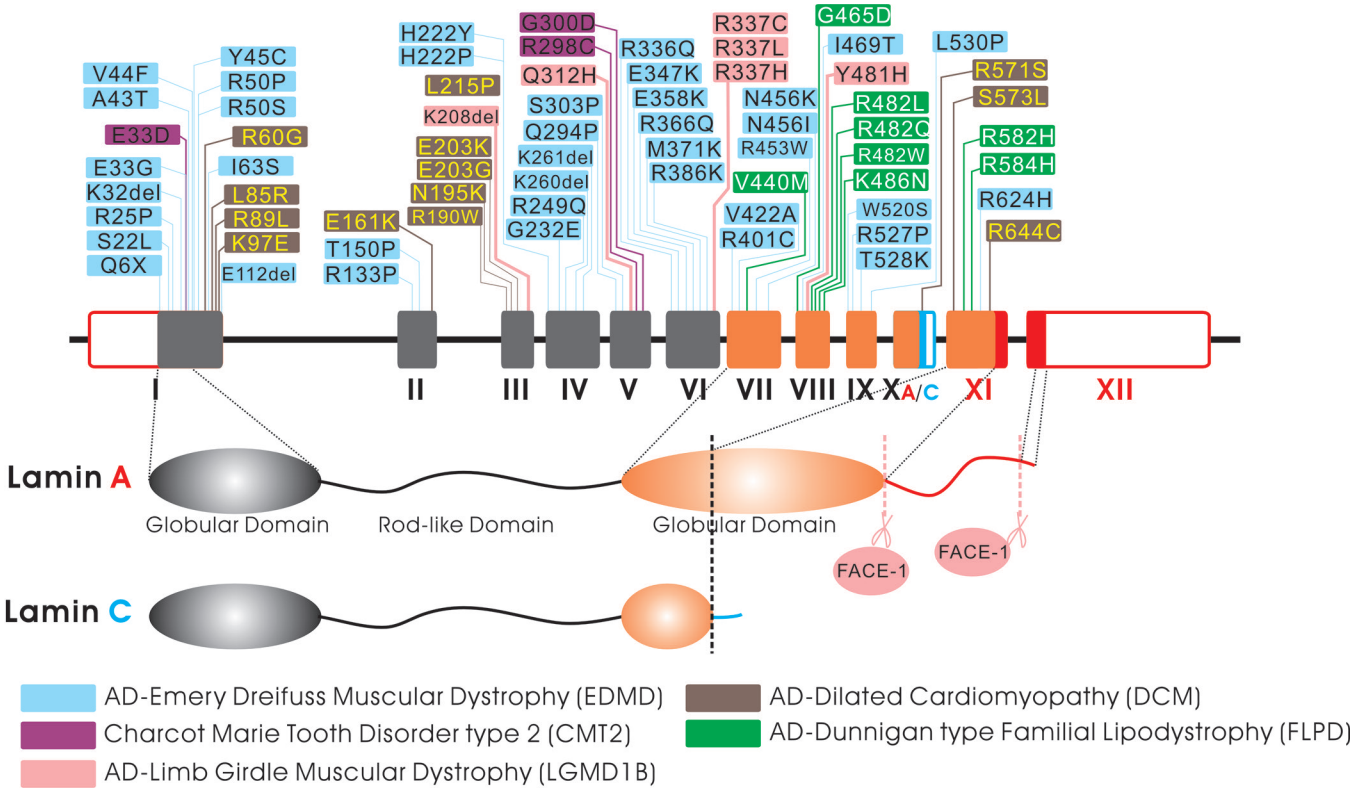

Fig. 5. *LMNA* mutations of non-progeroid laminopathies. *LMNA* mutations affect striated muscles in autosomal dominant Emery Dreifuss muscular dystrophy (EDMD), autosomal dominant limb girdle muscular dystrophy (LGMD1B) and autosomal dominant dilated cardiomyopathy (DCM); peripheral nerves in Charcot Marie tooth disorder type 2 (CMT2); and adipose tissues in autosomal dominant Dunnigan type familial lipodystrophy (FLPD).

as "progeria in childhood". The prevalence is about one in 8 million. So far, only about 100 patients have been reported, mainly in the Western world. Patients with HGPS can only survive for 12 to 16 years, with a mean age of 13.4 years. HGPS individuals are clinically characterized by early growth retardation, short stature, lipodystrophy, alopecia, stiff joints, osteolysis, dilated cardiomyopathy and atherosclerosis (Pollex and Hegele, 2004; Hennekam, 2006). A recurrent, *de novo*, dominant point mutation (1824 CT) of *LMNA* gene was identified to be responsible for about 76% of reported cases of HGPS. This mutation (p.G608G) activates a cryptic splicing donor signal in exon 11, leading to a 150 nucleotide deletion in mutant transcript, and a 50-residue truncation in the lamin A protein (Eriksson et al., 2003; Reddel and Weiss, 2004). The truncated lamin A retains the CAAX motif, but lacks the second proteolytic cleavage site of ZMPSTE24. A detailed study demonstrated that the mutant allele only expressed about 80% of total transcripts from the same allele and around 40% of total transcripts from both alleles (Reddel and Weiss, 2004). Shortly after, eight more different mutations of *LMNA* were reported in HGPS, with different severities, including E145K and G608S in autosomal dominant HGPS (De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003), K542N in combined autosomal recessive mandibuloacral dysplasia (MAD) and HGPS (Plasilova et al., 2004), E578V in autosomal dominant Werner's syndrome (WS) with mild HGPS (Csoka et al., 2004), Q567_Q656del in autosomal dominant RD with severe HGPS (Navarro et al., 2004), T623S (Fukuchi et al., 2004), R644C (Csoka et al., 2004) in autosomal dominant atypical HGPS, and R654X in combined HGPS and RD (Denecke et al., 2006).

Atypical Werner's syndrome

The history of WS can be traced back to 1904 when the first case was reported (Werner, 1904). WS is an autosomal recessive genetic disorder of "progeria in adulthood", affecting about 10 in one million (Multani and Chang, 2007). Patients suffering from WS were usually born healthy, with obvious growth retardation

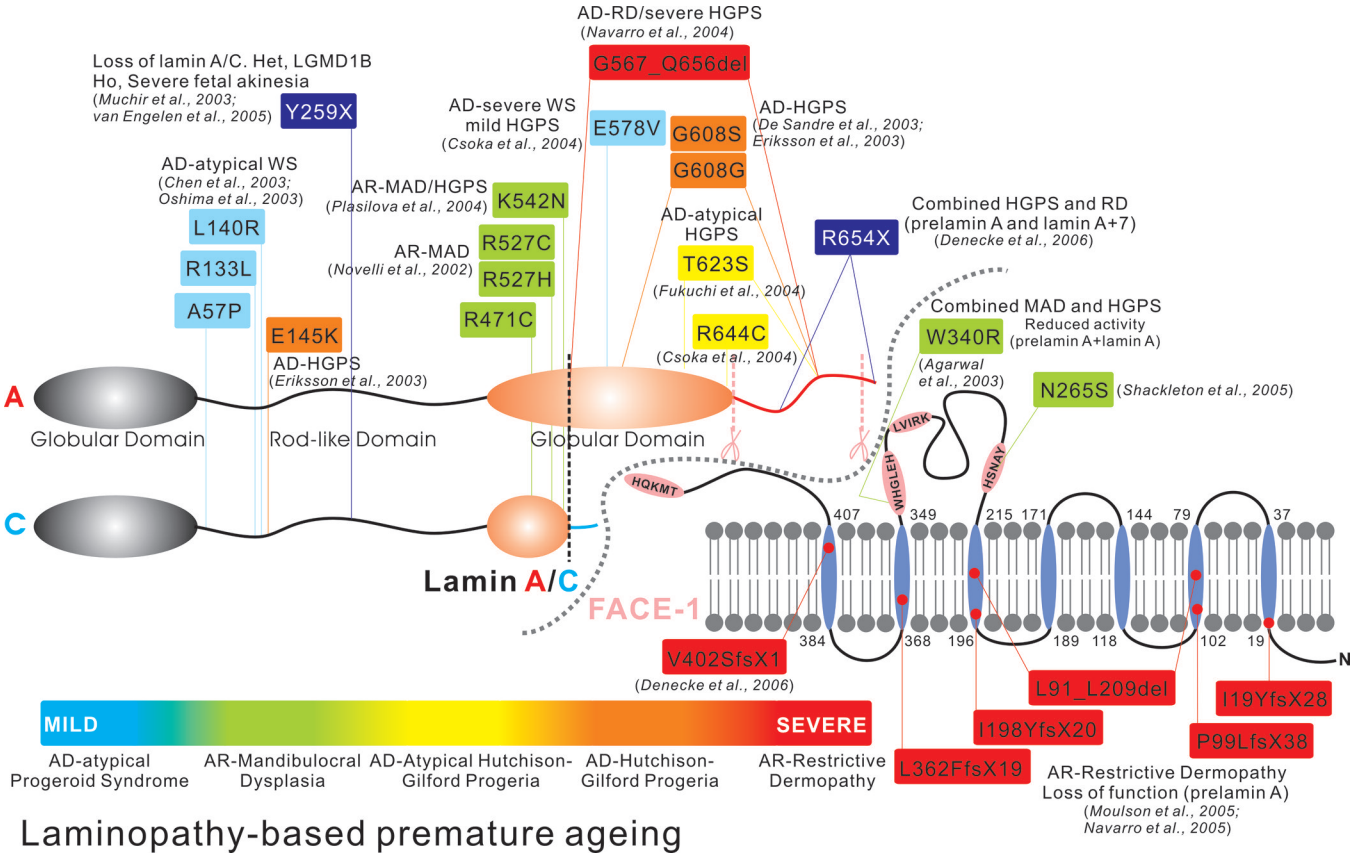

Fig. 6. Progeriod laminopathies. *LMNA* mutations were found to be responsible for a group of progeria syndromes, including autosomal dominant atypical Werner's syndrome (WS), autosomal recessive mandibulocral dysplasia (MAD), Hutchinson Gilford progeria syndrome (HGPS), autosomal recessive restrictive dermorpathy (RD) (also associated with unprocessed prelamin A caused by loss of function of ZMPSTE24) and autosomal recessive fetal askinesia.

from the second decade, and other ageing-related features, including short stature, premature cataract, beaked nose, skin atrophy and alopecia, loss of adipose tissues, type II diabetes, osteoporosis, arteriosclerosis, hypogonadism, and predisposition to cancer. WS patients typically die of early onset cardiovascular diseases or neoplasia in the fourth decade of life with an average life span of 47 years. Skin fibroblasts cultured from affected individuals developed accelerated senescence with increased chromosome aberrations (Salk et al., 1981; Melcher et al., 2000). By positional cloning, WRN was firstly linked to WS (Yu et al., 1996). Recently, lamin A/C mutations (A57P, R133L, L140R, and E578V) were also reported in autosomal dominant atypical WS, in which the affected individuals present more severe phenotypes compared to those associated with WRN (Chen et al., 2003; Csoka et al., 2004; Fukuchi et al., 2004).

Mandibuloacral dysplasia

MAD is a rare genetic autosomal recessive disorder with skeletal abnormalities, including hypoplastic mandible and clavicles, acroosteolysis, stiff joints, skin atrophy and lipodystrophy. While homozygous R527H (Novelli et al., 2002), K542N (Plasilova et al., 2004) and compound heterozygosity of R471C and R527C (Cao and Hegele, 2003) of *LMNA* were reported in MAD with type A lipodystrophy (MADA; OMIM 248370), only compound heterozygous mutations of ZMPSTE24 (Phe361fsX379 and W340R) were identified in MAD with type B lipodystrophy (MADB; OMIM 608612) (Agarwal et al., 2003).

Restrictive dermopathy

RD is a neonatal disorder characterized by tight adherent skin, joint contractures and respiratory insufficiency, together with features of the progeroid syndromes, and premature death during gestation. RD is usually associated with mutations that affected lamin A maturation, including *LMNA* mutations that disrupt prelamin A processing, and nullizygosity of ZMPSTE24, which causes unprocessed prelamin A accumulation. So far, only two lamin A mutations have been reported in RD combined with HGPS features, Q567_Q656del and R654X.

Lethal fetal akinesia

The first occurrence of human *LMNA* null mutation came from an LGMD1B family with Y259X nonsense mutation. While the heterozygous Y259X led to typical LGMD1B, the homozygous mutation resulted in lethal phenotypes after premature birth (van Engelen et al., 2005). The deceased newborn displayed dysmaturity, dysmorphic face and severe muscle atrophy (van Engelen et al., 2005). Studies in cultured skin fibroblasts demonstrated severe nuclear abnormalities, including misshapen nuclei, mislocalized lamin B_1/B_2, emerin, nesprin-1α and LAP2ß, and local absence of NPCs.

Secondary laminopathy caused by ZMPSTE24 mutationes

In human, mutations in prelamin A processing enzyme ZMPSTE24 were also associated with progeria, including autosomal recessive form of MAD and autosomal recessive lethal disorder – RD (Navarro et al., 2004, 2005; Levy et al., 2005; Moulson et al., 2005; Denecke et al., 2006). MAD is caused by compound heterozygous mutations of ZMPSTE24, a Phe361fsX379 mutation leading to a complete loss of function to process yeast α-factor in vitro, and another allelic Trp340Arg missense mutation adjacent to HEXXH motif with much less activity in processing α-factor. The same Phe361fsX379 mutation was also reported in RD but in a homozygous manner, which led to a complete loss of AAXing (the first proteolysis) activity of ZMPSTE24 (Corrigan, 2005) and accumulation of prelamin A. In agreement with this observation, other ZMPSTE24 mutations identified in RD, including V402SfsX1, L91_L209del, I198YfsX20, L362FfsX19, I19YfsX28 and P99LfsX38, are all homozygous mutations with a complete loss of function of at least one of the two proteolytic domains of ZMPSTE24, resulting in the accumulation of unprocessed prelamin A without mature lamin A. Compound heterozygous mutations in LMNA that retain a fraction of enzymatic activity in prelamin A processing, for example, a L362FfsX19 premature truncation and a N265S substitution, were linked to a severe MAD with mild RD phenotypes. Therefore, the phenotypic severity in MAD and RD seems to be correlated with the level of accumulated unprocessed prelamin A or the extent of prelamin A processing, with or without AAX. These observations, together with what has been found in *Zmpste24*$^{-/-}$ and *Lmna*$^{+/-}$*Zmpste24*$^{-/-}$ mice, suggested that unprocessed prelamin A underlies secondary laminopathies caused by ZMPSTE24 mutations; unprocessed prelamin A functions dominant-negatively in a dosage-dependent or an -AAX-dependent manner.

LMNA mutation position and disese severity in laminopathies

Although numerous mutations in *LMNA* were identified in various laminopathies, they are not evenly distributed across the gene, considering the affected organs and disease severity. Those affecting striated muscles and peripheral nerve systems are typically located in regions closer to the NH2 terminus, whereas those associated with lipodystrophy and premature ageing syndromes are distributed mostly in regions towards the COOH terminus. Among mutations in *LMNA* that cause progeriod syndromes, it is observed that the closer the mutation is to the COOH terminus, the more severe clinical features it gives rise to. Particularly,

mutations affecting prelamin A maturation usually lead to lethal RD (Fig. 7).

Mouse models resembling HGPS and other laminopathies

So far, there are three genetically modified mouse models phenotypically resemble HGPS, e.g. *Zmpste24*$^{-/-}$, *Lmna*$^{L530P/L530P}$ and *Lmna*$^{HG/HG}$ mice. In addition, three transgenic mouse lines have been developed to mimick laminopathy-based muscular dystrophy and cardiomyopathy in human. Table 1 summarizes the progeriod features shared between HGPS and the accelerated ageing mouse models.

Leung and colleagues (2001) for the first time generated *Zmpste24*-deficient mice to study the developmental role of *Zmpste24* in mouse. The exon 8 of mouse *Zmpste24*, encoding zinc-binding domain, was replaced by a neo cassette. Membranes purified from cells or tissues of *Zmpste24*$^{-/-}$ mice failed to cleave "-AAX" of yeast mating pheromone α-factor *in vitro* (Leung et al., 2001). Premature ageing phenotypes were documented later in a separate paper, where growth retardation, muscular weakness, hair loss, kyphosis, multiple spontaneous bone fractures, as well as reduced cortical and trabecular bone volumes by 6-8 weeks, and early death were described (Bergo et al., 2002).

Pendas et al. (2002) first described the progeriod phenotypes in *Zmpste24*$^{-/-}$ mice generated independently. In this mouse line, exon 2 and 3 of *Zmpste24* was replaced by an *IRES-β-GEO* cassette with a splice acceptor sequence. *Zmpste24*$^{-/-}$ mice were born indistinguishable from their wild-type and heterozygous littermates. However, progeriod phenotypes developed two months after in *Zmpste24*$^{-/-}$ mice. Growth retardation, fat and hair loss, abnormal dentition, cardiomyocyte fibrosis, dystrophic muscular fibers and decreased bone mineralization were noticed. Mutant mice died around 4-6 months of age. Both male and female *Zmpste24*$^{-/-}$ mice are sterile. Importantly, an accumulation of unprocessed prelamin A in the nuclear periphery, and abnormal nuclear morphology with herniations were observed in cultured mouse embryonic fibroblasts (MEFs) derived from *Zmpste24*$^{-/-}$ mice (Pendas et al., 2002). The introduction of human analogue of Zmpste24 cDNA into *Zmpste24*$^{-/-}$ MEFs eliminated the accumulation of prelamin A, suggesting that Zmpste24 is required for the processing of prelamin A *in vivo*. As prelamin A is so far the only identified substrate of Zmpste24, all the progeriod phenotypes observed in *Zmpste24*$^{-/-}$ are thought to be attributable to unprocessed prelamin A accumulation.

Lmna$^{L530P/L530P}$ mice were constructed initially to mimic Emery-Dreifuss muscular dystrophy (EDMD), as the L530P missense mutation was associated with EDMD in human (Raharjo et al., 2001; Mounkes et al., 2003). However, the substitution of Proline for Leucine at residue 530 in mouse lamin A/C resulted in either activation of an alternative splicing donor site after exon 9, which subsequently leads to either prematurely truncated lamin A/C protein (only exon 1-9) terminated with an extra 19 amino acids (lamin A/C$^{E536EfsX20)}$, or inactivated splicing of exon 9, resulting in deletion of the whole exon 9 (lamin A/C^{del9}) (Fig. 8) (Mounkes et al., 2003). While heterozygous mice with the L530P mutation are as healthy as wild-type littermates, homozygous mutants, although born indistinguishable from wild-type, developed severe growth retardation shortly after birth, and died around 4-5 weeks old (Forbes et al., 1983; Mounkes et al., 2003). *Lmna*$^{L530P/L530P}$ mice also developed many phenotypes resembling HGPS, such as abnormal dentition, loss of

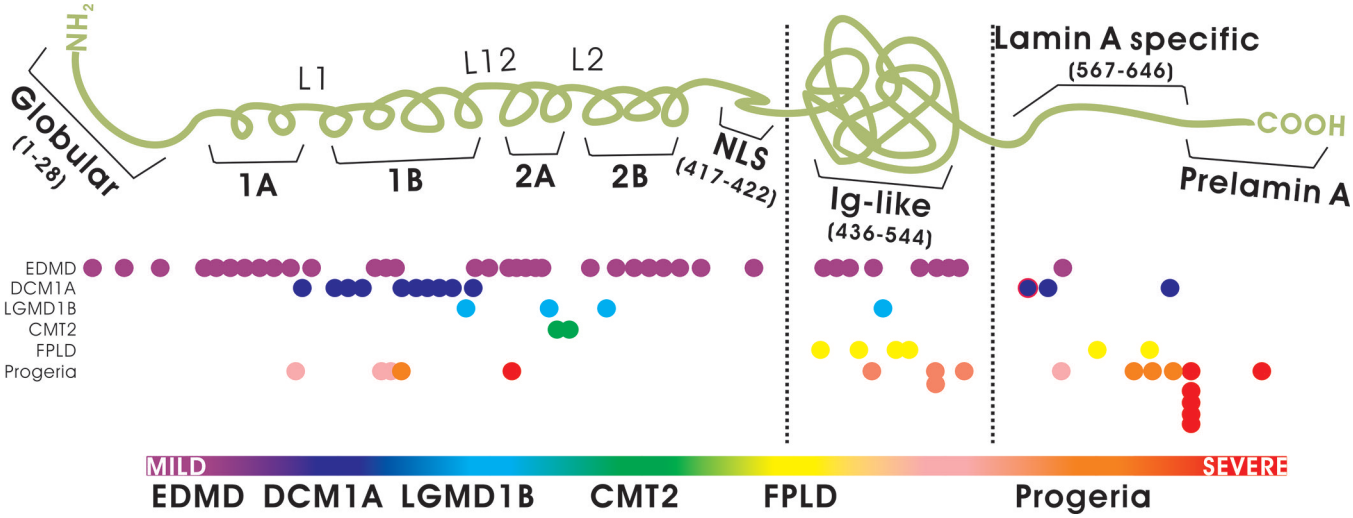

Fig. 7. *LMNA* mutation distribution and disease severity. *LMNA* mutations that affect striated muscles or peripheral nerve systems are typically located in regions closer to the N-terminus, whereas those associated with lipodystrophy or progeria are mostly located at the C-terminus.

subcutaneous fat, decreased bone density, waddling gait, muscular dystrophy, and hyperkeratosis.

Lmna$^{HG/+}$ was generated to mimic the HGPS mutation of *LMNA* (Yang et al., 2006). *Lmna*$^{HG/+}$ mice unaffected at birth, however, started to exhibit growth retardation by 3 weeks, loss of body weight by 6 to 8 weeks, and usually died before 27 weeks of age. The heterozygous mutant mice also developed other progeriod phenotypes similar to HGPS, including lipodystrophy, micrognathia, kyphosis of the spine, and osteoporosis. Spontaneous bone fractures were also observed in *Lmna*$^{HG/+}$ mice by 18 weeks of age. However, no abnormalities in skeletal muscles and aortas were observed in *Lmna*$^{HG/+}$ mice, which is different from *Zmpste24*$^{-/-}$ mice and human HGPS.

More severe progeriod features were observed in *Lmna*$^{HG/HG}$ mice. The homozygous mutants were small, with complete loss of body fat, spontaneous bone factures, decreased bone density and open cranial sutures. Cultured MEFs with misshapen nuclei were greatly increased in number in *Lmna*$^{HG/HG}$ mice compared to *Lmna*$^{HG/+}$.

Lmna$^{HG/-}$ mice were obtained by crossing *Lmna*$^{HG/HG}$ with *Lmna*$^{-/-}$ mice. The severity of the progeriod phenotype in *Lmna*$^{HG/-}$ mice was in between *Lmna*$^{HG/HG}$ and *Lmna*$^{HG/+}$ mice. All *Lmna*$^{HG/-}$ mice died by 10 to 14 weeks of age.

Sullivan and co-workers (1999) firstly established *Lmna*-deficient mice by deleting exon 8 until a part of

Table 1. Porgerial features in Hutchinson-Gilford progeria syndrome and premature ageing models.

HGPS	*Zmpste24*$^{-/-}$	*Lmna*$^{L530P/L530P}$	*Lmna*$^{HG/+}$
Short stature	Small body size	Extremely small size	Small body size
Growth retardation	Growth retardation from 4 weeks of age	Severe growth retardation from 2 weeks of age	Growth retardation at 4 weeks of age
Premature death, 12-16 years	4-6 months	4-5 weeks	27 weeks
Alopecia	Loss of hair on back	Decreased hair follicle	N/A
Osteoporosis	Osteoporosis	Osteoporosis	Decreased bone density
Cardiomyopathy	Cardiomyopathy	Cardiomyopathy	N/A
Abnormal dentition	Abnormal dentition	Abnormal dentition	N/A
Lipodystrophy	Loss of subcutaneous fat	Loss of subcutaneous fat	lipodystrophy
Muscular dystrophy	Muscular dystrophy	Muscular dystrophy	No obvious difference
Atherosclerosis	NA	No obvious difference	No obvious difference
Hyperkeratosis in some	Hyperkeratosis	Hyperkeratosis	N/A
Shuffling gaits	Waddling gaits from 2-3 months	Waddling gaits	N/A

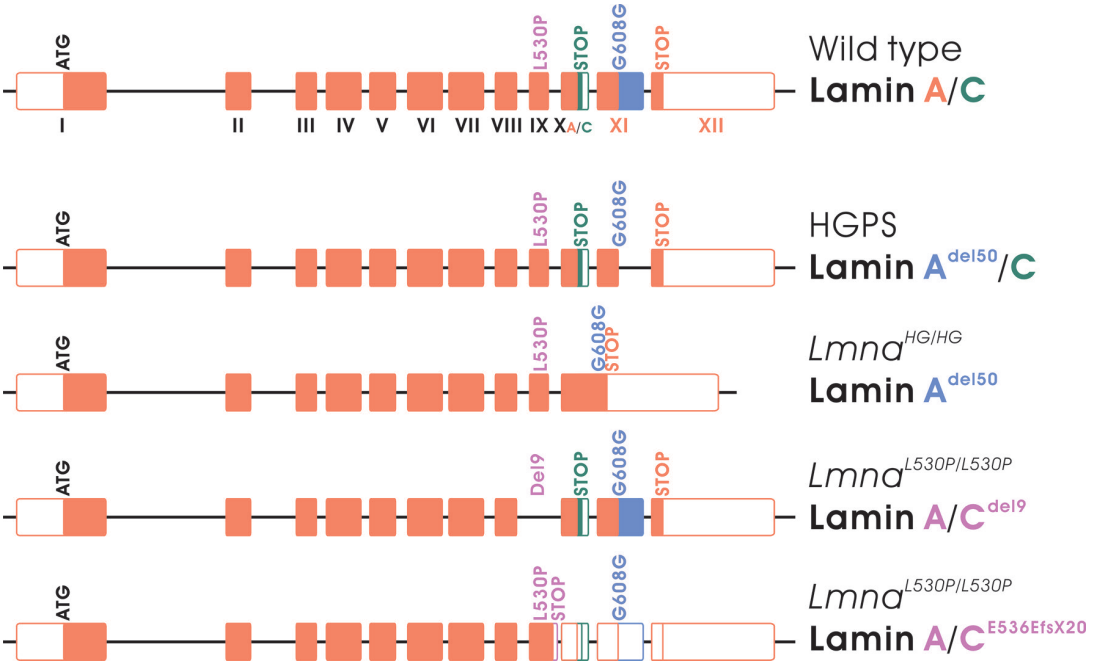

Fig. 8. Progerial A-type lamins in human and mouse models. In HGPS patients, the heterozygous *LMNA* G608G mutation results in a 50 amino acid deletion in prelamin A, so called progerin or lamin A$^{\Delta 50}$, which only constitutes 40% of total lamin A protein, whereas lamin C is hardly affected. *Zmpste24*$^{-/-}$ mice have unprocessed prelamin A and wild type lamin C. Lamin A/C in *Lmna*$^{L530P/L530P}$ mice is quite complicated, and is a mixture of lamin A/C^{del9} and lamin A/C^{E536EfsX20} (knock-in L530P mutation causes alternative splicing of mouse *Lmna* resulting in either a deletion of exon 9 or premature termination of lamin A/C protein).

exon 11, resulting in a complete loss of lamin A/C protein. Although born indistinguishable from wild-type littermates, homozygous lamin A/C mutant mice showed severe growth retardation shortly, and died of muscular atrophy and cardiomyopathy at around 6 to 8 weeks of age. Moreover, lamin A/C-deficient mice exhibited peripheral axonopathy with less, enlarged and nonmyelinated axons (De Sandre-Giovannoli et al., 2002). Recent studies also demonstrated that haplodeficiency of lamin A/C also developed cardiac conduction defects in *Lmna*$^{+/-}$ mice at about one year old (Burke and Stewart, 2006).

A second knock-in mouse line harboring H222P missense mutation, associated with autosomal dominant EDMD, was generated by Arimura et al. (2005). Male homozygous mutants displayed reduced locomotion and cardiac defects, including chamber dilation, hypokinesia, increased cardiac fibrosis, and usually died by 9 months of age. Female *Lmna*$^{H222P/H222P}$ mice exhibited exactly the same phenotypes except a later on-set date.

Lmna$^{N195K/N195K}$ knock-in is another mouse model that resembles human DCM-CD1 (Mounkes et al., 2005). Human N195K mutation was identified in DCM with conduction defects. Homozygous mutants died early and of arrhythmia before 3 months old, which is probably attributable to mis-regulation of transcription factors central to cardiac development and disruption of internal cardiac subcellular structures necessary for cardiac function (Mounkes et al., 2005).

Possible mechanisms undelrying laminopathy-baed premature ageing

Two hypotheses could explain how abnormal lamin A/C causes premature ageing – genomic instability and defective machenical stiffness. The genomic instability model proposes that unprocessed prelamin A in HGPS patients or *Zmpste24*$^{-/-}$ mice caused defective DNA repair and enhanced DNA damage checkpoint response, which in turn leads to accelerected cellular senescence. The mechanical stiffness hypothesis proposes that mutated lamin A/C compromises the stiffness of the nuclear skeleton in response to mechanical stress.

Defective maintenance of genomic integrity

Studies on *Zmpste24*$^{-/-}$ mice and HGPS fibroblasts revealed that unprocessed prelamin A compromise genome integrity, which might in turn lead to premature ageing in human and mouse. *Zmpste24*$^{-/-}$ mouse embryonic fibroblasts (MEFs) showed increased micronuclei and aneuploidy, and exhibited hypersensitivity to DNA damaging agents, especially to those which can introduce double-strand breaks (DSBs) (Liu et al., 2005). In addition, *Zmpste24*$^{-/-}$ mice were much more sensitive to γ-irradiation. *Zmpste24*$^{-/-}$ MEFs and HGPS dermal fibroblasts showed a delayed resolve of fragmented DNA upon massive DNA damage, probably due to defective recruitment of DNA repair proteins, including p53 binding protein 1 (53BP1) and Rad51. Although the exact molecular mechanism is still poorly understood, it is plausible to speculate that lamin A/C may serve as a platform for DNA damage response and DNA repair. In line with detective DNA repair is the observation of the highly activated p53 pathway in Zmpste24 knockouts compared to wild-type littermates. Downstream targets of p53, including *Gadd45α*, *p21, PA26, Btg2, Atf3, Rtp801* and *Rgs16* etc, were substantially up-regulated, although no obvious changes were observed in p53 expression and modifications (Varela et al., 2005). When crossed to p53 null background, the *Zmpste24*$^{-/-}$*p53*$^{-/-}$ compound mutants live longer and have higher body weight compared to *Zmpste24*$^{-/-}$ mice. The life-span and cellular senescence in MEFs and tissues were also significantly increased and rescued respectively (Varela et al., 2005).

Impaired mechanics and mechanotransduction

Lamin A/C is a major component of the nucleoskeleton, which guarantees nuclear mechanical stability and mechanotransduction to support basic nuclear activities. Studies from Lammerding et al. (2004) demonstrated that a loss of lamin A/C resulted in impaired nuclear mechanics and mechanotransduction, and *Lmna*$^{-/-}$ fibroblasts were more sensitive to mechanical strain (Lammerding et al., 2004). Further studies in *Lmna*$^{-/-}$ and *Lmna*$^{-/-}$ cells indicated that both lamin A and C are required for maintaining nuclear stiffness, and mechanically activated gene expression, whereas lamin B_1 is important for nuclear integrity (Lammerding et al., 2006). In HGPS dermal fibroblasts, A-type lamins seemed to be trapped in the nuclear periphery and formed orderd microdormains, which made the cells unable to dissipate mechanical stress like healthy ones (Dahl et al., 2006). Different lamin A/C mutations could affect the mechanical functions to different extents, which in turn result in different phenotypes observed in laminopathies.

Therapeutic strategies for laminopathy-based premature ageing

Progerin is generated by aberrant splicing of the *LMNA* gene. Scaffidi and Misteli (2005) designed morpholino oligos specific to the cryptic splicing site in exon 11, which were transfected into HGPS dermal fibroblasts by electroporation. The aberrant mRNA and subsequent progerin were largely diminished, and the misshapen nuclear morphology, as well as altered histone modifications and gene expression, were significantly rescued. Using a similar strategy, RNA interference specific for pre-spliced mutated *LMNA* mRNA successfully reduced progerin by 26% or more, and the misshapen nuclei, slow cell proliferation rate, and cellular senescence were significantly ameliorated (Huang et al., 2005).

HGPS fibroblasts and *Zmpste24*$^{-/-}$ MEFs are

characterized by abnormal nuclear morphology with blebbings, herniations and disorganized heterochromatin, which are speculated to be the result of an accumulation of unprocessed prelamin A on the nuclear lamina. The loss of the second proteolytic cleaving site in progerin or the absence of processing enzyme in *Zmpste24*$^{-/-}$ mice resulted in the retention of a farnesylcysteine terminus, which may disrupt the nuclear lamina integrity. Hence, the removal of unprocessed prelamin A from the nuclear rim might restore the deformed nuclear morphology. Recently, this idea was tested by several groups, and they found that the incubation of FTIs with HGPS fibroblasts, *Zmpste24*$^{-/-}$ MEFs or Hela cells transfected with unprocessable prelamin A could diminish the isoprenylation of progerin and unprocessed prelamin A, and acumulating them to the nucleoplasm, and most significantly the misshapen nuclear envelopes can be largely rescued (Capell et al., 2005; Columbaro et al., 2005; Mallampalli et al., 2005; Toth et al., 2005; Yang et al., 2005). More interestingly, feeding *Zmpste24*$^{-/-}$ and *Lmna*$^{HG/+}$ mice with FTIs significantly restored most of the misshapen nuclei, increased body weight and prolonged life-span (Fong et al., 2006a; Yang et al., 2006). Although administration of FTIs can significantly rescue deformed morphology in both HGPS and *Zmpste24*$^{-/-}$ cells, and partially restore body weight and life-span in both *Zmpste24*$^{-/-}$ and *Lmna*$^{HG/+}$ mice, the underlying mechanisms are still unclear to date. While the removal of unprocessed prelamin A from nuclear lamina can restore the nuclear morphology, this might not be a direct effect of defarnesylation of prelamin A, rather due to defarnesylation of B-type lamins, since lamin A/C does not depend on farnesylation of itself for lamina association but, most probably, depends on B-type lamins whose assembly into lamina relies on farnesylation. So it can be speculated that FTIs-treatment might have a side effect that both B-type and A-type lamins aggregate to the nucleoplasm.

Compromised heterochromatin organization in HGPS might dysregulate gene expression, which might be one of the possible mechanisms underlying premature ageing. Columbaro and colleagues (2005) showed that both facultative and constitutive heterochromatin was affected in all investigated HGPS fibroblasts, characterized by reduced monomethylated and trimethylated H3K9 (H3K9me and H3K9me3). A combined treatment of farnesylation inhibitor mevinolin and histone deacetylase (HDAC) inhibitor, such as trichostatin A (TSA), can significantly reduce progerin level and restore heterochromatin organization (Columbaro et al., 2005), although the mechanism undelying this rescue is not clear.

Perspectives

Mutations in DNA repair proteins, lamin A/C, or its processing enzyme ZMPSTE24 cause premature ageing. Delineating the possible mechanism of premature ageing would be helpful to our understanding of the molecular mechanisms of natural ageing. Recently, studies conducted by different groups indicated that physiological ageing might also share a similar pathway to premature ageing. Studies in *Caenorhabditis elegans* by Haithcock et al. (2005) showed that aged cells exhibited similar nuclear morphological defects to HGPS; it seemed to be related to insulin/IGF-1-like signaling pathway. An investigation from Scaffidi and Misteli (2006) demonstrated that the same cryptic splicing site giving rise to progerin in HGPS was also activated in normal fibroblasts, and cells from aged people also exhibited altered chromatin modification and increased DNA damage. In the damage accumulation theory of ageing, cells and tissues are constantly exposed to a variety of environmental and endogenous conditions that can lead to tissue damage. While most of the DNA damage can be successfully repaired, some accumulate, and the accumulation may result in cellular senescence, which eventually leads to organism ageing (Halliwell and Whiteman, 2004; Tanaka et al., 2006). In line with this, we observed accelerated accumulation of DNA damage in laminopathy-based premature ageing, such as *Zmpste24*-deficient mice. Although the precise mechanism is still poorly understood, it is plausible that abnormal lamin A proteins compromise chromatin structure, which in turn leads to defective DNA repair in cellular senescence and organismal ageing.

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