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Lamin A, farnesylation and aging

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Abstract

Lamin A is a component of the nuclear envelope that is synthesized as a precursor prelamin A molecule and then processed into mature lamin A through sequential steps of posttranslational modifications and proteolytic cleavages. Remarkably, over 400 distinct point mutations have been so far identified throughout the *LMNA* gene, which result in the development of at least ten distinct human disorders, collectively known as laminopathies, among which is the premature aging disease Hutchinson–Gilford progeria syndrome (HGPS). The majority of HGPS cases are associated with a single point mutation in the *LMNA* gene that causes the production of a permanently farnesylated mutant lamin A protein termed progerin. The mechanism by which progerin leads to premature aging and the classical HGPS disease phenotype as well as the relationship between this disorder and the onset of analogous symptoms during the lifespan of a normal individual are not well understood. Yet, recent studies have provided critical insights on the cellular processes that are affected by accumulation of progerin and have suggested that cellular alterations in the lamin A processing pathway leading to the accumulation of farnesylated prelamin A intermediates may play a role in the aging process in the general population. In this review we provide a short background on lamin A and its maturation pathway and discuss the current knowledge of how progerin or alterations in the prelamin A processing pathway are thought to influence cell function and contribute to human aging.

Keywords

Lamin A; Progeria; Farnesylation; Laminopathies

Lamins and their processing pathway

Lamins are a family of nuclear proteins that belong to the intermediate filaments [1,2]. Humans have two types of lamins, types A and B. A-type lamins (lamin A and C) are generated by alternative splicing of the RNA transcribed from the *LMNA* gene, while B-type lamins (lamins B1 and B2) are encoded by distinct transcripts originating from the *LMNB1* and *LMNB2* genes. There are two additional and less characterized A-type lamins:

lamin C2, which was identified in human germ cells [3,4], and is identical to Lamin C, except for its amino terminal region that is encoded by an alternative exon located in the first intron of the *LMNA* gene, and lamin A 10, which has been detected in many cell types and tissues and is a lamin A isoform generated by exon 10 skipping. While B-type lamins are constitutively expressed in every cell, A-type lamins are expressed only after gastrulation in a tissue-specific manner. Lamins are primarily localized near the inner side of the nuclear membrane where they interact with membrane-associated proteins to form the nuclear lamina, a protein-rich region of the nucleus adjacent to the nuclear membrane. B-type lamins and lamin A but not lamin C are synthesized with a conserved CaaX (cysteine–aliphatic amino acid–aliphatic amino acid–any amino acid) motif in their carboxyl terminal ends that is subjected to sequential processing steps to generate the mature forms of lamin A, lamin B1 and lamin B2 (Fig. 1) [5,6]. First a farnesyltransferase adds a 15-carbon farnesyl isoprenoid to the carboxyl terminal cysteine (CaaX). Farnesylated lamins are then modified by a prenyl-CaaX-specific endoprotease that removes the tripeptide at the carboxyl terminus of prelamin A and lamin B. RAS converting enzyme 1 (RCE1) is responsible for the cleavage of the peptide in B-type lamins, while RCE1 as well as ZMPSTE24, the Zn metallopeptidase that is also required for the final proteolytic step of prelamin A, have been implicated in the cleavage of the -SIM tail from prelamin A [7]. The carboxyl terminal farnesylcysteine is then methylated by an isoprenylcysteine carboxyl methyltransferase (ICMT). While B-type lamins are permanently farnesylated and carboxymethylated, prelamin A undergoes an additional step mediated by ZMPSTE24, which cleaves the carboxyl terminal 15 amino acids releasing the mature, unfarnesylated and unmethylated lamin A. It is intriguing that the carboxyl terminal tail of lamin A undergoes extensive modifications before being cleaved off, and the precise role of these processing events is not well understood. As farnesylation and carboxymethylation increase the hydrophobicity of a protein, it is likely that these modifications facilitate the accurate targeting of the final lamin A product to the nuclear envelope. Yet, there is evidence that mature lamin A generated by bypassing the processing steps is incorporated into the nuclear lamina, although with distinct kinetics [8–10]. The fate of the carboxyl terminal peptide released by ZMPSTE24 cleavage is unclear, and it could remain anchored to the membrane or be rapidly degraded.

Lamin A mutations and disease

The *LMNA* gene is a hotspot for disease-causing mutations and has received a remarkable amount of attention because of its association with a variety of human diseases. More than four hundred mutations spanning the protein-coding region of the *LMNA* gene have been identified to date (<http://www.umd.be/LMNA>). Some of these mutations are within the region of the *LMNA* gene encoding for both lamin A and C, while others are unique for lamin A. These mutations cause the onset of many distinct disorders, collectively termed laminopathies, which include Emery–Dreifuss Muscular dystrophy (EDMD), limb girdle muscular dystrophy type 1B (LGMD1B), dilated cardiomyopathy (DCM), autosomal recessive Charcot-Marie-Tooth type 2 (CMT2), Dunnigan type familial partial lipodystrophy (FPLD), mandibuloacral dysplasia with type A lipodystrophy (MADA), Hutchison–Gilford progeria syndrome (HGPS), atypical Werner Syndrome (aWS) and restrictive dermopathy (RD) [11]. Some of the diseases resulting from mutations in the

LMNA gene affect multiple tissues while others have a strict tissue-specificity, with mutations in flanking amino acid residues often leading to disorders with distinct pathologies. One of the most striking and devastating among the laminopathies is the accelerated aging disease HGPS [12]. HGPS is a rare disease that is observed in about 1 in 4 million children worldwide [12,13], which is caused by *de novo* germline mutations in the *LMNA* gene [14,15]. The disease is diagnosed soon after birth and is characterized by a plethora of pathologies including severe growth retardation, micrognathia, abnormal dentition, osteoporosis and bone hypoplasia, gonadal defects, lipodystrophy, atherosclerosis and skeletal muscle atrophy [16]. Children with HGPS typically die due to cardiac failure between the age of 13 and 16 years old. At least 20 distinct mutations in the *LMNA* gene have been linked to HGPS, however the most frequent is a point mutation at position 1824 that activates a cryptic splice site donor [14,15]. This leads to the production of a mutant prelamin A protein with an internal 50 amino acid deletion lacking the terminal ZMPSTE24 cleavage site but not affecting the C-terminal CaaX motif. As a consequence, the mutant HGPS prelamin A, which has been termed progerin, remains permanently farnesylated and carboxymethylated [17]. Two murine models of HGPS have been generated by either the use of a human BAC clone containing the entire *LMNA* gene with the c.1824C>T mutation or a mouse knock-in allele that produces exclusively progerin [18,19]. Interestingly the two mice models are characterized by a non-overlapping set of phenotypes. The BAC transgenic mice show defects in the smooth-muscle cells of the vascular system, but none of the systemic progeria-related disease phenotypes (such as skeletal abnormalities, alopecia, growth retardation, reduced survival) while the second mice model displays several progeria-like phenotypes including severe growth retardation, abnormal dentition, kyphosis and fragile bones. However, these mice do not demonstrate vascular defects, cardiomyopathy, muscle atrophy and weakness, which also characterize HGPS.

Altered prelamin A metabolism disrupts cell function

The production of progerin leads to the progressive appearance of a number of cellular alterations including severe growth defects and altered nuclear membrane morphology that collectively manifest as an early onset of an aging phenotype. The affected children generally succumb to cardiovascular problems and similarities between many aspects of cardiovascular disease in progeria patient and normal adult individuals with atherosclerosis have recently been reported [20]. Ectopic expression of progerin in normal diploid fibroblasts recapitulates most if not all the phenotypes of progeria cells suggesting that the mutant protein acts in a dominant negative manner. It is not surprising that mutations in the *ZMPSTE24* gene, whose product is required for the last cleavage step in the prelamin A processing pathway that affect the activity or synthesis of this protein, cause MAD and RD, respectively, two progeria-like human diseases characterized by growth retardation, skeletal abnormalities and cutaneous atrophy [21–23]. The relationship between these diseases of accelerated aging and the onset of analogous symptoms during the lifespan of a normal individual is unclear. Yet, studies have suggested that aberrant splicing of the prelamin A RNA leading to the production of progerin may play a role in general human aging [24,25]. Furthermore, alterations in the normal prelamin A processing pathway have also been implicated in aging of the vascular system in the absence of progerin, as demonstrated by a

recent study showing that prelamin A accumulates in vascular smooth muscle cells (VSMCs) of aged individuals but not of young individuals [26]. Here, the accumulation of prelamin A is the result of a decrease in the levels of ZMPSTE24, suggesting an age-dependent decline in the activity of this critical processing enzyme. The idea that the normal pathway that produces mature lamin A is a finely poised system is supported by cell-based studies which demonstrated that perturbations affecting the kinetics of prelamin A maturation can drive cells into an accelerated aging phenotype [27], a concept further supported by studies in animals [28]. These studies point to the permanently farnesylated carboxyl-terminal tail of prelamin A as the toxic moiety, which is consistent with studies showing that ectopic expression of prelamin A variants that are constitutively farnesylated results in the formation of lamin A aggregates and altered nuclear membrane morphology, and severely limited cell growth, in a manner similar to progerin [8,29]. To determine whether blocking the farnesylation of the carboxy terminal tail in progerin and prelamin A can relieve cellular toxicity, several groups have tested short term inhibition of protein farnesylation by treatment of cells with farnesyl transferase inhibitors (FTIs). These studies demonstrated that nuclear morphology defects and cell proliferation are reversed, at least in part, in progeria cells as well as cells expressing ectopic progerin or elevated levels of prelamin A after FTI treatment [19,27,30–33]. The implication of these findings is that unfarnesylated progerin and prelamin A are better tolerated than the farnesylated counterparts. However, even though FTIs have been proven safe and do not induce toxicity on the short term, accumulation of unfarnesylated progerin and prelamin A by blocking protein farnesylation may have undesired outcomes over a longer period of time. Indeed, cell-based experiments demonstrated that a subpopulation of cells expressing a variant of prelamin A that cannot be farnesylated over a period of several months display changes in nuclear morphology that are accompanied by reduced levels of the transcription factor TBP [8]. Treatment of differentiating myoblast with mevinolin, an HMG-CoA reductase inhibitor that by preventing the synthesis of the farnesyl lipid leads to the accumulation of the unfarnesylated prelamin A, leads to alterations in the subcellular localization of envelope proteins and the positioning of nuclei in myotubes [34]. Furthermore, mice expressing lamin A-SSIM, a form of prelamin A that cannot be farnesylated, ultimately develop cardiac disease [35]. It is also important to point out that FTI treatment is preventing farnesylation of other cellular proteins, thus influencing other cellular processes including proliferation, apoptosis, differentiation, transcription, and immune response independently of prelamin A accumulation [36,37].

Nuclear processes influenced by altered prelamin A metabolism

The molecular basis of the toxicity induced by partially processed forms of prelamin A is poorly understood but structural as well as functional deficiencies are likely to contribute to the onset of the defective phenotypes. First, lamin A is thought to provide a mechanical framework for the support of the nuclear envelope [38,39] and accumulation of progerin or farnesylated prelamin A may cause abnormalities in the structure of the nuclear membrane and render the cell more susceptible to damage caused by physical stress [40]. This is consistent with the observation that progerin-expressing cells show signs of mechanical stress and increased fragility of the nucleus [41,42]. While this model may explain some of

the phenotypes observed in progeria cells, it is evident that lamin A, by controlling nuclear structure, is also influencing fundamental nuclear processes either indirectly, or by making direct contacts with chromatin and transcription factors (Fig. 2). It is documented that accumulation of progerin alters the functional organization of chromosomes by causing changes in the distribution and levels of heterochromatin as well as abnormal telomeres length homeostasis [24,43–46]. These epigenetic changes are likely to influence gene expression, as evident from the large number of genes that are expressed differentially in HGPS cells as compared to normal cells [47–50]. Remarkably, heterochromatin organization can be recovered by combined treatment with inhibitors of farnesyltransferase and histone deacetylases, suggesting that these changes can be reversed by pharmacological treatment [51–53]. Progerin has not been reported to interact with or directly influence histone acetyltransferases or deacetylases, yet altered levels or localization of other regulators of chromatin structure, including RBBP4 and 7, two components of the NURD chromatin remodeling complex, and ING1, a tumor suppressor and regulator of histone modifying enzymes, have been observed in progeria cells [54,55]. These findings suggest that changes in these and possibly other chromatin remodeling and modifying factors contribute to the alteration in the epigenetic organization of chromatin induced by progerin.

Lamin A has been shown to bind several transcription regulators, including the Kruppel-like protein MOK2 [56], the sterol response element-binding protein SREBP1 [57], the retinoblastoma protein (Rb) [58], and c-Fos [59], and these interactions influence the localization and function of these factors. Lamin A interaction with MOK2 has been shown to promote the association of a subpopulation of this factor with the nuclear matrix and expression of pathogenic mutants of lamin A results in the sequestration of MOK2 into nuclear aggregates [60]. The interaction of lamin A with Rb, a tumor suppressor and regulator of the activity of the E2F family of transcription factors that is required for activation of expression of genes required for entry into S phase of the cell cycle, plays an important role in protecting pRb from proteosomal degradation [61]. The interaction of lamin A with c-Fos, a cellular proto-oncogene which dimerizes with c-Jun to form the AP-1 transcription factor, results in the sequestration of this factor to the nuclear envelope, thus causing the repression of AP1 activity [59]. There is also biochemical evidence that partially processed prelamins A sequesters SREBP1 to the nuclear lamina whereas pathogenic lamin A mutants induce the aggregation of SREBP1 into nuclear foci [62,63]. Whether accumulation of progerin influence the localization of this set of transcription factors and changes in their activity contribute to the onset of progeria has not been investigated extensively. However data from genome wide expression profiling studies indicate that progerin expression is accompanied by alteration in the expression of genes whose expression is regulated by Rb, and these changes are reversed upon FTI treatment [64]. Transcriptome studies, although not always concordant possibly because of differences in the experimental set up, have been quite helpful in providing insights on pathways influenced by progerin. One study found alterations in the levels of factors that function downstream of the Notch signaling pathway, suggesting that progerin may influence cell fate decisions and cell differentiation processes during embryonic as well as adult life [49]. A second study demonstrated reduced nuclear localization of the transcription factor LEF1, a transcription factor involved in WNT signaling, in progeroid cells, ultimately affecting the

synthesis of a functional extracellular matrix [65]. Collectively these studies underscore the concept that accumulation of progerin influences the levels and spatial localization of transcriptional regulators, which, in combination with changes in the epigenetic make up of the chromatin, is likely to contribute to the altered landscape of gene expression observed in progeroid cells.

Progeria cells undergo a short period of hyperproliferation followed by apoptosis and senescence [27,66] and activation of p53 is a key feature of progeria cells, cells with defective prelamin A processing pathway (*Zmpste24* knockout mice) and cells expressing ectopic progerin [67,68]. Therefore activation of a p53-dependent signaling pathway is likely to play a critical role in growth inhibition by progerin. Consistent with this hypothesis, inhibition of p53 function improves growth of progerin-expressing cells as well as reestablishes the proliferation capacity of cells from *Zmpste24* knockout mice [29,68]. However, the precise mechanism of p53 activation and whether this activation is linked to both premature senescence and apoptosis in progerin-expressing cells remains to be established. DNA damage may be an inducer of p53 since progeria cells as well as cells from progeria mice models display phosphorylated histone 2AX (γ H2AX) foci, a marker of DNA breaks [24,67,68]. In cultured fibroblasts, p53-dependent senescence or apoptosis could be triggered in response to DNA damage triggered by either telomere attrition or dysfunctional DNA repair, as both processes activate a DNA damage-signaling pathway [69,70]. Published data suggest that both processes may contribute to growth dysfunction induced by progerin. First, fibroblasts expressing progerin display altered telomere length homeostasis [45,46] and γ H2AX has been localized at telomeres in these cells [71], suggesting that deprotection of telomere ends could be the process triggering p53-dependent senescence or apoptosis. Intriguingly, a recent study has suggested a novel reciprocal relationship between telomere dysfunction and progerin production, which may be relevant to the normal aging process [72]. Second, it has been shown that the Xeroderma Pigmentosum group A (XPA) DNA repair protein is aberrantly recruited to DNA double-strand breaks (DSB) in progeria cells [73]. Notably, depletion of XPA partially restores DSB repair in progeria cells, suggesting that mislocalization of XPA plays a significant role in the inhibitory process.

Concluding remarks

Can the information gained so far be utilized for the development of therapeutic approaches to treat the diseases caused by accumulation of farnesylated mutants or intermediate forms of prelamin A? The finding that most of the effects induced by the accumulation of farnesylated prelamin A or progerin are reversible is rather gratifying, as it makes it possible to devise strategies that target the production or stability of the toxic moiety. Clinical trials that are testing the efficacy of drugs that inhibit the synthesis of the farnesyl lipid substrate or prevent addition of the farnesyl moiety to progerin are underway in both the US and Europe and their outcome is anxiously awaited. In addition, the realization that mice lacking both lamin A and C develop disease and die within 8 weeks from birth, while mice expressing only lamin C do not display any obvious phenotype and have a normal life span [74], can be exploited for the development of approaches that target the production of prelamin A without affecting lamin C. Clearly, still much remains to be understood about

progeria, the relationship between this disease and normal aging, and how distinct tissues and organs are influenced by altered prelamin A metabolism. Significantly, whereas most of what we learned to date about progeria and the culprit protein progerin has been accomplished through studies that utilize fibroblast lines, three labs have recently reported the generation of induced pluripotent stem cell (iPSC) lines from progeria fibroblasts [75–77]. Remarkably, progeria iPSC lines downregulate progerin expression and revert many of the defective phenotypes observed in fibroblasts, which are then restored upon differentiation. As these cell lines can be differentiated into distinct lineages, they can provide unique information on how specific organs and tissues respond to progerin expression, and thereby significantly improve our knowledge on the biology of lamins, the pathogenesis of progeria and its relationship to physiological aging.

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Fig. 1. Domain organization and structure of precursors and mature forms of human lamin A, B and C. Schematic representation of the basic structures of precursors for lamin A and B, their mature products, and lamin C. The carboxy-terminal peptide released by cleavage of prelamin A by ZMPSTE24 is also shown although its cellular fate is unknown. The regions spanning the conserved alpha helical rod and Ig fold domains are shown by the double-headed, solid arrows.

Fig. 2.

Possible mechanisms by which accumulation of progerin or prelamin A intermediates lead to accelerated aging. Mutations in the *LMNA* gene leading to the synthesis of progerin or alterations in the processing pathway causing the accumulation of farnesylated prelamin A intermediates affect the function of several nuclear processes that induce cell dysfunction and result in the onset of an accelerated aging phenotype. See text for discussion.