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Invited Review Article

Premature aging syndromes: From patients to mechanism

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ABSTRACT

Aging is an inevitable consequence of human life resulting in a gradual deterioration of cell, tissue and organismal function and an increased risk to develop chronic ailments. Premature aging syndromes, also known as progeroid syndromes, recapitulate many clinical features of normal aging and offer a unique opportunity to elucidate fundamental mechanisms that contribute to human aging. Progeroid syndromes can be broadly classified into those caused by perturbations of the nuclear lamina, a meshwork of proteins located underneath the inner nuclear membrane (laminopathies); and a second group that is caused by mutations that directly impair DNA replication and repair. We will focus mainly on laminopathies caused by incorrect processing of lamin A, an intermediate filament protein that resides at the nuclear periphery. Hutchinson-Gilford Progeria (HGPS) is an accelerated aging syndrome caused by a mutation in lamin A and one of the best studied laminopathies. HGPS patients exhibit clinical characteristics of premature aging, including alopecia, aberrant pigmentation, loss of subcutaneous fat and die in their teens as a result of atherosclerosis and cardiovascular complications. Here we summarize how cell- and mouse-based disease models provided mechanistic insights into human aging and discuss experimental strategies under consideration for the treatment of these rare genetic disorders.

1. Lamina-associated progeroid syndromes: laminopathies

The eukaryotic nucleus is defined by a double-layered structure consisting of the inner and outer nuclear membrane. Underneath the inner nuclear membrane lies a 15–20 nm thick proteinaceous meshwork made of type V intermediate filament proteins, the A- and B-type lamins. A-type lamins A, AΔ10, C and C2 are alternative splice forms derived from the *LMNA* gene, whilst B-type lamins B1 and B2 originate from *LMNB1* and *LMNB2* genes, respectively [1]. A-type lamins are not expressed in the haematopoietic system and are largely absent from the central nervous system, whilst B-type lamins are expressed in all nucleated human cells. This differential expression, in part, provides an explanation why lamin-associated mutations afflict some tissues but not others. Lamins form a regulatory nexus involved in facilitating fundamental cellular processes, including heterochromatin organisation, DNA replication and repair, and nucleocytoplasmic transport [1,2] (Fig. 1). Wild type pre-lamin A is subject to several post-translational processing steps; first, a farnesyltransferase attaches a 15-carbon farnesyl isoprenoid lipid moiety to the cysteine of pre-lamin A's C-terminal CAAX motif, thereby anchoring pre-lamin A into the nuclear membrane. The last 15 amino acids (including the farnesylated tail) are then proteolytically cleaved by the metalloendoprotease ZMPSTE24, also known as FACE-1, to form mature lamin A and allow its incorporation into the nuclear lamina [3]. Mutations in lamin A that affect its post-translational processing, or in proteins involved in lamin A processing, result in the accumulation of lamin A precursors with severe cellular and organismal consequences. Such perturbations or mutations of the nuclear lamina cause a variety of human diseases, including muscular dystrophies, lipodystrophies and the progeroid syndromes Restrictive Dermopathy (RD), Mandibuloacral Dysplasia (MAD), Néstor-Guillermo Progeria Syndrome (NGPS) and most prominently Hutchinson-Gilford Progeria Syndrome (HGPS), collectively called laminopathies (Table 1).

2. Atypical Werner syndrome

Werner syndrome (WS) is an adult onset progeroid syndrome caused by an autosomal recessive mutation in the *RECQL* DNA helicase gene. Patients exhibit signs of premature aging in their twenties, including hair greying, alopecia, skin atrophy, ulcers and

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impaired growth, and die as a result of cardiovascular disease or cancer. However, roughly 20% of patients clinically diagnosed with WS do not carry *WRN* mutations, but harbour mutations in the *LMNA* gene. 24 such *LMNA* mutations have been identified to data and these patients are classified as atypical Werner syndrome (AWS) or atypical progeroid syndrome (APS) [4,5,6,7].

3. Atypical progeroid syndromes: restrictive dermopathy

Restrictive dermopathy (RD) is a very severe lethal neonatal disease characterized by tightly adherent and translucent skin, dermal thinning, disorganized collagen fibers and an almost complete loss of elastic fibers in the dermis. The first signs of RD appear during gestation and include severe intrauterine growth defects, reduced fetal movement and pre-term delivery [8]. A common characteristic among laminopathies is that many are caused by an accumulation of unprocessed pre-lamin A. In the case of RD, this is either caused by loss of function mutations in *ZMPSTE24* or by mutations in lamin A, that remove the ZMPSTE24-specific proteolytic cleavage site. A skin biopsy obtained from a patient carrying a *ZMPSTE24* mutation revealed increased nuclear size and an atrophic epidermis with focal hyperkeratosis and hypoplastic sebaceous glands. Lastly, patient cells exhibited nuclear abnormalities that became worse with extended *in vitro* culture and a mislocalization of other lamina-associated proteins [8].

4. Mandibuloacral dysplasia

A milder form of RD is Mandibuloacral dysplasia (MAD): MAD type A is characterized by partial lipodystrophy, aberrant skin pigmentation, partial alopecia, skeletal abnormalities, insulin resistance and impaired growth. MAD type B patients exhibit alopecia, abnormal skin pigmentation, lipodystrophy, insulin resistance and severe skeletal abnormalities [9]. MAD type A can be caused by lamin A mutations that interfere with its post-translational processing, whilst MAD type B is caused by compound heterozygous mutations in ZMPSTE24 that lower its catalytic activity, both resulting in an accumulation of unprocessed lamin A. On a cellular level, MAD is associated with nuclear abnormalities, thickening of the nuclear lamina and heterochromatin loss [9].

5. Néstor-Guillermo progeria syndrome

An example of a progeroid syndrome that is not caused by mutations involved in lamin A processing is Néstor-Guillermo progeria syndrome (NGPS). NGPS is characterised by early onset of

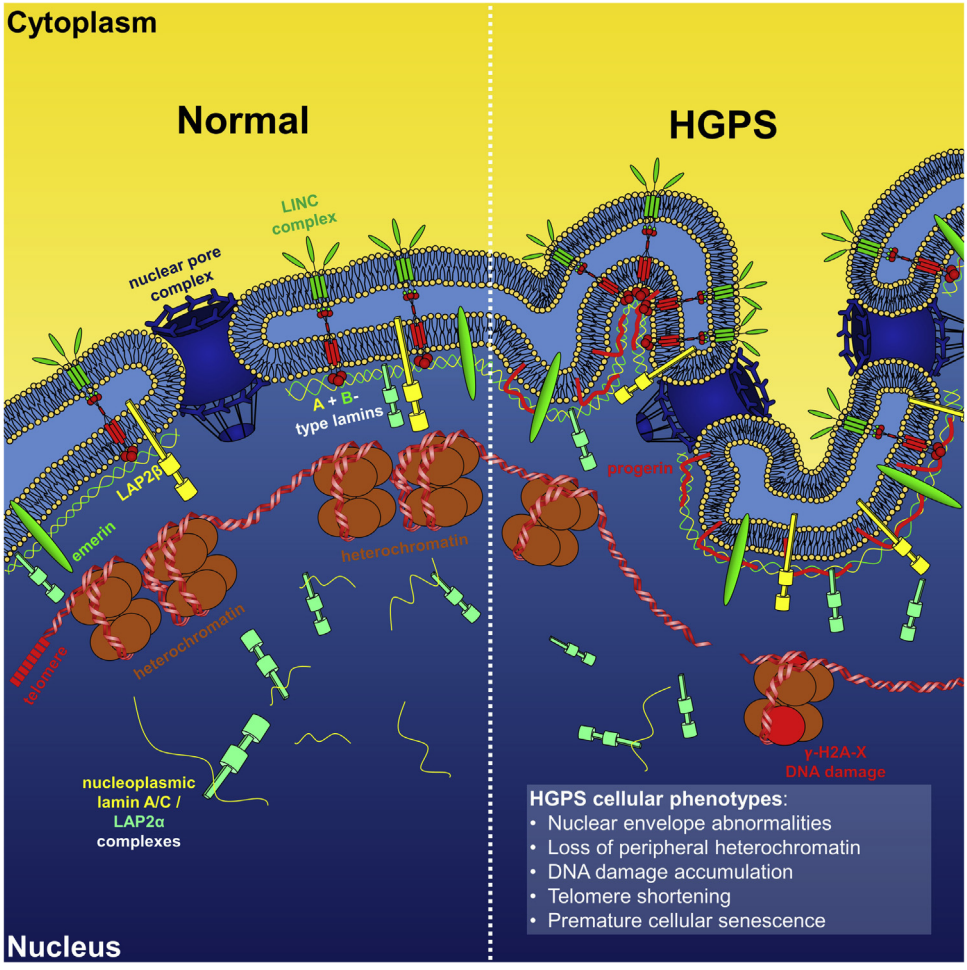

Fig. 1. Schematic representation of a normal (left) and HGPS (right) nucleus.
The nucleus is defined by a double-layered structure consisting of an inner and outer nuclear membrane. The nuclear lamina lies underneath the inner nuclear membrane and consists of intermediate filament proteins, the A- and B-type lamins, and associated proteins (only emerin and LAP2ß are shown). Cytoplasm and nucleoplasm are connected via the LINC complex. Progeria is caused by a mutated form of lamin A, called progerin, that remains permanently farnesylated and membrane-bound (red filaments, right panel). Progerin expression alters nuclear architecture and results in loss of peripheral heterochromatin (H3K9 trimethylation and H3K27 trimethylation loss), DNA damage (as shown by accumulation of γ-H2A-X (red histone), telomere shortening, and premature cellular senescence.

Table 1
Organismal and cellular phenotypes of progeroid syndromes.

Disease	Gene / Mutation	Organismal Phenotype	Cellular Phenotype	References
Restrictive dermopathy	*LMNA* *ZMPSTE24*	Neonatal lethal, intrauterine growth defect, tightly adherent and translucent skin, dermal thinning, aberrant organisation of collagen fibers.	Nuclear envelope deformities, mislocalisation of lamins and lamina-associated proteins.	Navarro 2004
Mandibuloacral dysplasia type A	*LMNA*	Onset at 4-5 years after birth, partial lipodystrophy, thin and rigid skin, aberrant skin pigmentation, bone and growth defects, insulin resistance.	Nuclear envelope deformities, thickened nuclear lamina, mislocalisation of lamina-associated proteins, peripheral heterochromatin loss.	Novelli 2002, Agarwal 2003, Filesi 2005, Cenni 2018
Mandibuloacral dysplasia type B	*ZMPSTE24*	Onset at 2 years of age, lipodystrophy, altered skin pigmentation, alopecia, severe bone and growth defects, insulin resistance.	Nuclear envelope deformities, proliferation defects.	Agarwal 2003, Cenni 2018
Néstor-Guillermo progeria syndrome	*BANF1*	Onset at 2 years of age, altered skin pigmentation, lipodystrophy, growth and severe bone defects, alopecia, lack of cardiovascular complications.	Nuclear envelope deformities, mis-localisation of emerin.	Puente 2011, Cabanillas 2011
Hutchinson-Gilford progeria syndrome	*LMNA*	Onset by 12-18 months old, sclerotic skin, lipodystrophy, altered skin pigmentation, alopecia, bone and growth defects, cardiovascular complications, death in mid-teens.	Nuclear envelope deformities, mislocalisation of lamins and lamina-associated proteins, peripheral heterochromatin loss, impaired nucleocytoplasmic transport, increase in DNA and telomere damage, premature senescence, impaired cellular differentiation.	Eriksson 2003, De-Sandre-Giovannoli 2003, Allsopp 1992, Bridger and Kill 2004, Goldman 2004,Liu 2005, Liu 2006, Shumaker 2006, Decker 2009, Chojnowski 2015, Merideth 2008
Atypical progeroid syndrome / atypical Werner syndrome	*LMNA*	Late onset: mid to late 30's. Sclerotic skin, hair greying & alopecia, loss of subcutaneous fat, altered skin pigmentation, cardiovascular disease.	Nuclear envelope deformities, aberrant heterochromatin organization (aggregation and loss).	Chen 2003, Hisama 2011, Doubaj 2012, Motegi 2014

aging-associated phenotypes including alopecia, altered pigmentation, growth defects, severe skeletal abnormalities and lipoatrophy [10,11]. In contrast to other progeroid syndromes such as Hutchinson-Gilford progeria (described below), NGPS progresses more slowly, patients do not exhibit cardiovascular complications and have a relatively longer lifespan [11]. NGPS is caused by a homozygous A12 T mutation in *BANF1*, which encodes the Barrier to Autointegration Factor 1 (BAF). BAF is a nuclear lamina-associated protein that binds DNA and is involved in chromatin organisation and post-mitotic nuclear assembly. Fibroblasts derived from NGPS patients exhibit reduced BAF protein levels, whilst mRNA levels remain unaffected, nuclear abnormalities and a relocalization of emerin from the nuclear envelop to the cytoplasm. Although the precise molecular mechanism how this BAF mutation triggers premature aging remains unclear, it is of particular interest as NGPS patients share similar clinical features as patients with Hutchinson-Gilford progeria, yet do not suffer from cardiovascular disease [11].

6. Hutchinson-Gilford progeria syndrome

Arguably the best studied laminopathy is Hutchinson-Gilford progeria (HGPS), a syndrome characterized by a precocious appearance of aging-related features. HGPS manifests itself ~12–18 months after birth and is characterized by growth and bone defects, loss of joint mobility, lipodystrophy, alopecia, sclerotic skin, altered pigmentation (hyper- and hypopigmentation), and loss of subcutaneous fat. Patients succumb in their mid-teens as a result of atherosclerosis and cardiovascular complications [12]. Progeria is caused by a *de novo* heterozygous silent point mutation in *LMNA* (c.1824C > T; G608 G), that activates a cryptic splice site in exon 11 and results in an in-frame deletion of 50 amino acids near its C-terminus [13,14]. Whilst the mutation does not affect the alternative splice variant of *LMNA*, lamin C, the truncated mutant form of lamin A is known as progerin (Fig. 2A). Progerin lacks the ZMPSTE24 cleavage site and remains permanently farnesylated, resulting in impaired incorporation into the nuclear lamina and nuclear shape abnormalities.

The critical role of appropriate lamin A processing was highlighted by a patient, whose clinical features resembled those of HGPS, but lacked the classical G608 G *LMNA* mutation [15]. Instead, the patient carried a homozygous null mutation for *ZMPSTE24* and a heterozygous *LMNA* mutation (c.1960C > T, R654X). The *LMNA* mutation generated a truncated form of lamin A that lacked the C-terminal CAAX motif essential for the addition of the farnesyl moiety. As described above, a homozygous ZMPSTE24 mutant would normally result in RD and early neonatal death. However, in this particular case, the mutated *LMNA* allele resulted in a non-farnesylatable version of lamin A, thereby causing a milder phenotype that resembled HGPS [15].

RD, MAD and HGPS are all caused by an accumulation of unprocessed or mutated and permanently farnesylated lamin A. To prevent the constitutive farnesylation of progerin, farnesyltransferase inhibitors (FTI), such as Ionafarnib have been used *in vitro*, in multiple progeria mouse models, as well as in a clinical trial as a potential therapeutic for the treatment of HGPS [16]. FTI treatment ameliorated nuclear shape abnormalities *in vitro*, but resulted in limited improvement in HGPS patients [16]. A possible explanation is that FTI treated progerin is subsequently geranylgeranylated and retains its toxicity. In agreement with this notion, treatment with compounds that block both farnesylation and geranylgeranylation, such as statins (pravastatin) and aminobisphosphonates (zoledronate) improved aging-associated phenotypes in a progeria mouse model and are currently under investigation for the treatment of HGPS [17,18]. Nevertheless, it must be noted that mice expressing a non-farnesylatable version of progerin still developed similar phenotypes, suggesting that progerin also disrupts cellular processes, irrespective of its farnesylation status [19].

Lastly, inhibition of the mammalian target of rapamycin (mTOR) pathway by rapamycin results in a lifespan extension in

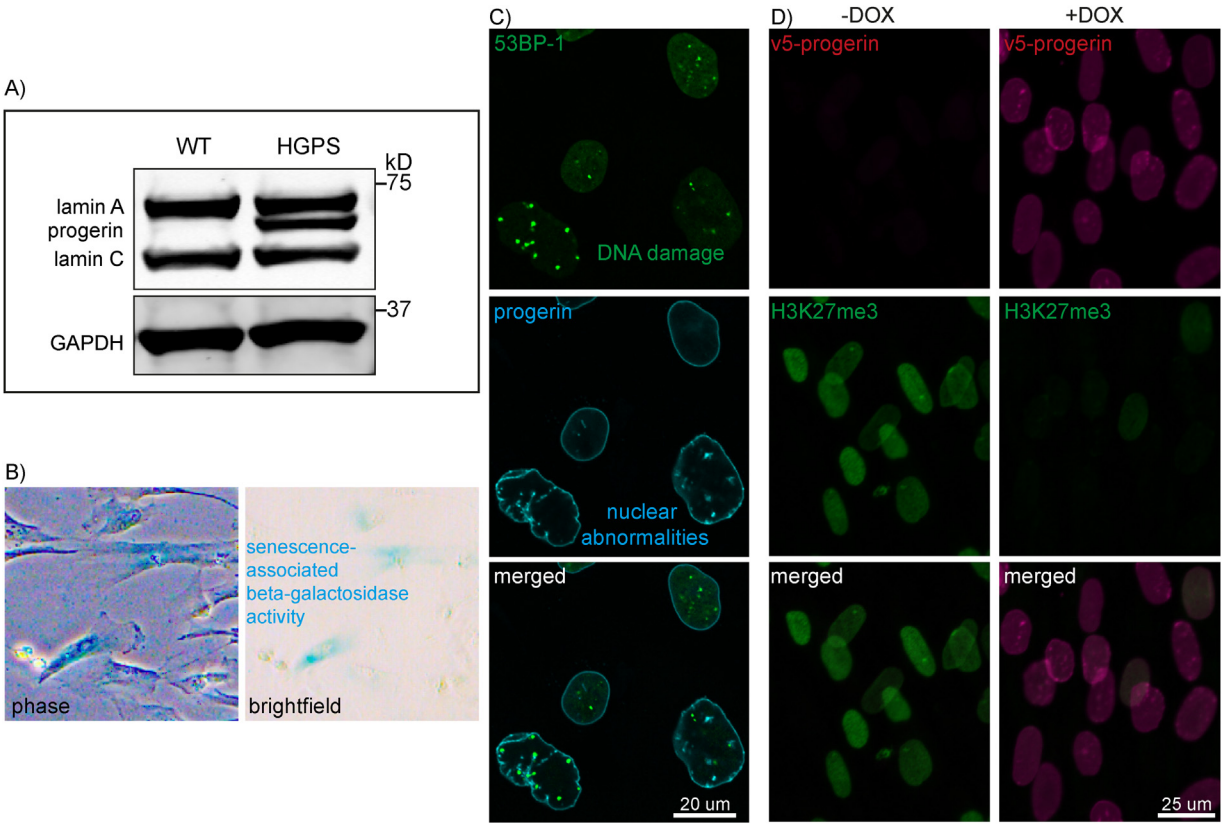

Fig. 2. Progerin-induced cellular phenotypes. A) Western blot showing progerin expression in HGPS fibroblasts. Lamin A, progerin, lamin C and GAPDH are shown. (B) Progerin-expressing cells undergo premature senescence and stain positive for senescence-associated β-galactosidase staining (blue color). (C and D) Immunofluorescence images showing (C) abnormal nuclear architecture and DNA damage (53BP-1) in cells expressing v5-tagged progerin (v5-progerin). (D) Progerin expression causes heterochromatin loss: Doxycycline-inducible v5-progerin triggers loss of heterochromatin mark H3K27me3. v5-progerin and H3K27me3 are shown in cells treated in the presence (+DOX) or absence (-DOX) of progerin. Size markers are indicated.

Drosophila, mouse and nematodes. Similarly, treatment of HGPS cells with rapamycin or its analog everolimus enhanced autophagy and progerin turnover and ameliorated progerin-induced nuclear shape abnormalities and proliferation defects [20,21].

7. Cellular consequences of progerin expression

On a cellular level progerin expression results in a variety of defects including changes in nuclear shape, a thickened nuclear lamina, DNA damage, genomic instability, telomere shortening, heterochromatin loss, aberrant nucleocytoplasmic transport and premature senescence (Figs. 1 and 2) [22–26]. A key challenge is to understand how these different phenotypes are functionally and causally linked – and whether they are a cause or a consequence of premature senescence.

8. Impaired nucleocytoplasmic transport

A number of studies reported that progerin expression interferes with nucleocytoplasmic transport. Ran is a guanosine triphosphate GTPase that facilitates transport of cargoes across the nuclear pore. Ran is GTP bound in the nucleus and GDP bound within the cytoplasm, forming a gradient between these two cellular compartments. Progerin expression perturbs this Ran gradient and interferes with faithful transport of cargoes through the nuclear pore. As a result, key mediators of the DNA damage response (DDR), including ataxia telangiectasia protein kinase (ATM) and γ-H2A-X, exhibit impaired translocation into the nucleus. Pre-lamin A expression similarly interferes with nuclear entry of 53BP-1, another key factor of the DDR [27]. Collectively, defective transport of these factors may impair DDR signalling and DNA repair. Treatment with a small molecule inhibitor of the N-acetyltransferase 10 (NAT10), termed Remodelin, restored the localization of Ran and 53BP-1 and ameliorated various progerin-induced phenotypes *in vitro*, as well as in a progeria mouse model *in vivo* [26,27].

9. Heterochromatin loss

Fibroblasts from progeria patients, chronologically aged human cells, as well as cells ectopically expressing progerin exhibit loss of peripheral heterochromatin, as shown by electron microscopy and loss of histone H3 lysine 9 and 27 trimethylation (H3K9me3 and H3K27me3) [22,23]. The mechanism how progerin triggers such widespread chromatin changes remains debated. Early studies showed that heterochromatin loss is associated with reduced levels of heterochromatin protein 1α, a factor that binds H3K9me3, as well as several chromatin remodelling factors, including the enhancer of Zeste homologue 2 (EZH2) - a H3K27-specific methyltransferase - and components of the nucleosome remodelling and deacetylase (NuRD) complex [23,28]. However, a more recent study comparing the expression of epigenetic modifiers in wild type versus progerin expressing mouse skin found no significant changes [29]. Nevertheless, knockdown of components of the NuRD complex recapitulated some aspects of HGPS including loss of H3K9me3 and accumulation of DNA damage [30]. Taken together, the mechanistic and temporal relationship between progerin expression, a possible misregulation of histone modifiers, heterochromatin loss and DNA damage require further investigation.

10. DNA damage

Progeria-patient derived fibroblasts and normal cells forced to express progerin accumulate DNA damage, exhibit a chronic activation of DNA damage checkpoints, undergo premature senescence and exhibit senescence-associated transcriptional changes [22,24]. Progerin-induced DNA damage has been suggested to be a result of impaired DNA repair, replicative or oxidative stress, or accelerated telomere shortening and dysfunction [22,24,25,31].

Early studies suggested that progerin expression impairs the recruitment of repair factors to sites of DNA damage [24,32], possibly as a result of impaired nuclear import of DNA repair factors, as described above. However, it was recently found that progerin expression *per se* does not result in a higher mutation rate, implying that progerin may not interfere directly with DNA repair processes [33]. It has also been reported that progerin sequesters NRF2, a key factor that protects cells from oxidative stress, thereby resulting in increased reactive oxygen species, DNA damage and premature aging [34]. In addition, several studies provided evidence that progerin and pre-lamin A sequester PCNA, an essential component of the DNA replication complex, resulting in replication stalling and subsequent collapse of replication forks [35–37].

The persistent activation of DNA damage checkpoints in HGPS fibroblasts could also be caused by critically shortened or dysfunctional telomeres. Telomeres protect chromosome ends from illegitimate DNA repair that would otherwise result in circularization and fusion of chromosomes. Consequently, DNA damage caused by critically shortened telomeres cannot be repaired by conventional DNA repair processes, results in persistent DNA damage checkpoint activation and is associated with many age-related medical conditions [38].

Indeed, HGPS patient derived fibroblasts have significantly shorter telomeres than their age-matched controls [22,25]. Interestingly, telomere length varied greatly between different chromosomes with no bias towards shortening of any particular chromosome end. This suggests that telomere shortening in HGPS fibroblasts may be caused by more stochastic events, rather than an increased rate of telomere attrition during each replicative cycle [25]. In addition, telomere shortening was not observed in hematopoietic cells, which are devoid of lamin A (and thus progerin) expression, indicating that telomere attrition is a direct consequence of progerin expression [25]. In agreement with these findings, Benson and colleagues found that progerin-induced DNA damage co-localizes with components of the telomere-associated shelterin complex [31]. To investigate whether telomeric DNA damage plays a critical role in progerin-induced premature senescence, we recently modulated the DDR specifically at telomeres [39].

The DDR is orchestrated by a cascade of events that facilitate cell cycle arrest and recruit repair factors to the site of DNA damage. This process is initiated by phosphorylation of the histone variant H2A-X by the ATM. The secondary recruitment of DNA damage response factors (responsible for DNA repair) depends on long non-coding RNAs (dilncRNAs) generated by RNA polymerase II. dilncRNAs are then processed by the endoribonucleases DROSHA and DICER into shorter RNAs, termed DNA damage response RNAs (DDRNAs), that recruit the secondary DDR factors. By using sequence specific antisense oligonucleotides (ASOs), the DDR can be abolished at specific sites within the genome. In collaboration with the d'Adda di Fagagna group, we recently demonstrated that telomere specific ASOs alleviate progerin-induced telomeric DNA damage and premature senescence [39].

DNA damage due to critically shortened telomeres can also be circumvented by the expression of telomerase, a reverse transcriptase that uses an RNA moiety to add telomeric repeats onto telomeres. Endogenous and ectopic expression of telomerase, or transient introduction of telomerase RNA, prevented progerin-induced DNA damage and premature senescence in several cell-based model systems [22,31,40]. It is worth noting that telomerase is only active at telomeres during S-phase. This implies that in order for telomerase to repair or prevent progerin-induced DNA damage, it is likely to have occurred during DNA replication, which is in agreement with studies reporting that progerin interferes with DNA replication [35–37]. Taken together, these results demonstrate that telomere dysfunction plays an important role in progerin-induced DNA damage and premature senescence.

But what is the connection between perturbations of the nuclear lamina and telomere dysfunction? In a number of organisms, including yeast, *Trypanosoma brucei* and *Plasmodium falciparum*, telomeres are tethered to the nuclear periphery [41]. In contrast, the spatial localization of human telomeres in relation to the nuclear lamina is less clear. The first possible interaction between telomeres and the nuclear lamina was reported in 1990: Purified lamin A and C, but not lamin B, bound oligonucleotides consisting of human TTAGGG telomere repeats *in vitro*. Two years later, nuclear fractionation experiments by Titia de Lange suggested that human telomeres are attached to insoluble remnants, that included components of the nuclear lamina [41]. More recent work from our group suggested that ~40-50% of telomeres localize within 250 nm of the nuclear lamina [22]. In particular, telomeres are transiently enriched at the nuclear periphery during nuclear reassembly and early G1 [42] and both the lamina-associated polypeptide α (LAP2α) and BAF transiently localize to telomeres during nuclear assembly (more about LAP2α later) [43]. Perturbations of the nuclear lamina, such as depletion of lamin A/C (in mouse embryonic fibroblasts (MEFs)) led to a redistribution of telomeres from the nuclear periphery towards the nuclear interior and increased their mobility. In contrast, telomere mobility appeared to be impaired in fibroblasts from HGPS patients [41]. Taken together, although these studies point towards a role of the nuclear lamina in impacting the spatial organization and movement of telomeres within the nucleus, it is unclear whether telomeres are actively tethered to the lamina by specific factors or whether they simply package at the periphery within the context of heterochromatin. In addition, it remains to be determined whether the relative position of a telomere within the nucleus determines its susceptibility to progerin-induced DNA damage.

Lastly, it is important to note that telomerase expression does not prevent progerin-induced nuclear abnormalities or heterochromatin loss [22]. A more comprehensive rescue of progerin-induced phenotypes was achieved by overexpression of LAP2α [22,44]. Ectopic expression of LAP2α in progerin-expressing fibroblasts restored heterochromatin levels, prevented DNA damage and restored their proliferative capacity [22]. In a second study, LAP2α's restorative potential was linked to regulation of extracellular matrix (ECM) genes and dependent on its nucleoplasmic interaction with lamin A [44,45]. In agreement with these findings, lamin A/C interacts directly with chromatin and LAP2α and has been suggested to play an important role in chromatin organization and compaction [46]. The interaction between LAP2α and lamin A is impaired in HGPS, as a result of progerin's C-terminal truncation [22]. Moreover, LAP2α interacts with the N-terminus of high mobility group N5 (HMGN5), a protein involved in chromatin compaction [47]. Although speculative at this point, it is possible that progerin distorts the interplay between wild type lamin A, LAP2α and HMGN5, thereby resulting in chromatin decompaction and heterochromatin loss. Further supporting this notion, a C-terminal LAP2α mutation that compromised its binding to lamin A/C, is associated with familial dilated cardiomyopathy, suggesting that the interaction between lamin A and LAP2α plays a

central role in the pathophysiology of HGPS and possibly other laminopathies [48].

Collectively, these examples illustrate the broad spectrum of progerin-induced cellular defects and highlight the challenge to understand whether and how these different phenotypes are temporally and causally linked with each other.

11. Mouse models of progeria

A number of excellent progeroid mouse models have been generated to explore the consequences of mutations in *Lmna* or defective lamin A processing on an organismal level (reviewed in [17]). One of the first mouse models was generated by deleting Zmpste24, the endoprotease responsible for removal of the farnesyl moiety from pre-lamin A. Zmpste24-deficient mice accumulated unprocessed pre-lamin A, DNA damage, persistent activation of p53 and prematurely senescent cells. Among other phenotypes, homozygous mice exhibited loss of subcutaneous adipose tissue, atrophic epidermis and loss of hair follicles. Crossing these mice into a p53-deficient background partially reversed most of these phenotypes, providing evidence for the detrimental consequences of pre-lamin A accumulation and persistent DDR activation [49].

Another progeroid mutant mouse was generated by a splice defect that resulted in a 40 amino acid C-terminal deletion in lamin A (*Δ9Lmna*) [1]. Although this mutant form of lamin A remains constitutively farnesylated like progerin, it is expressed only at ~10% of wild type lamin A. Homozygous *Δ9Lmna* mice show no overt phenotype at birth, but develop rapid loss of subcutaneous fat, growth retardation, reduced hair follicle density and died 3–4 weeks after birth. *Δ9Lmna* MEFs phenocopied some aspects of HGPS patient cells including shortened telomeres and heterochromatin alterations [1]. In addition, mouse adult fibroblasts from *Δ9Lmna* mutant mice exhibited reduced synthesis of ECM components and impaired proliferation, the latter being alleviated by growing *Δ9Lmna* fibroblasts on a layer of ECM, produced by wild type fibroblasts [1].

To more accurately recapitulate HGPS, a mutant mouse was generated in which both alleles of *Lmna* were replaced by c.1827C > T; G609 G, which is the mouse equivalent of the human *LMNA* c.1824C > T mutation [50]. Homozygous mice developed age-related phenotypes including loss of subcutaneous fat deposits and hair loss 3 weeks after birth. Further analysis revealed a marked accumulation of unrepaired DNA damage and senescent cells within several tissues [50]. Treatment with an antisense morpholino that blocked aberrant *Lmna* splicing reduced the accumulation of progerin in tissues, restored subcutaneous fat, reduced the number of senescent cells and significantly extended the lifespan of these mice [50]. Lastly, both the *Zmpste24-/-* and $Lmna^{G609G/G609}$ mutant mice exhibited increased NF-κB activation and accumulation of inflammatory cytokines (possibly due to the accumulation of senescent cells), that could be partially rescued by genetic or pharmacological modulation of NF-κB signalling [51]. More recently, the López-Otín laboratory developed a CRISPR/Cas9-based approach in conjunction with an adeno-associated virus 9-based delivery to disrupt $Lmna^{G609G/G609}$ upstream of its HGPS mutation. Although the delivery efficacy was modest and limited to some tissues, the approach resulted in a significant median lifespan extension and ameliorated progerin-associated defects [52].

To specifically investigate the consequences of progerin expression in skin and hair follicles, the Eriksson lab generated a mouse model in which progerin was placed under the control of tetracycline-inducible promotor in keratin 5 (K5)-expressing interfollicular epidermis (IFE) and hair follicles [53]. The doxycycline-inducible system enabled the authors to temporally restrict the timing and dosage of progerin expression. Similar to the doxycycline-inducible *in vitro* cell culture system, low levels of progerin did not result in any discernible skin phenotype [22,53]. Depending on the onset of progerin-expression, day 0 or day 21, the median survival of these mice was 7 or 14 weeks, respectively. In both instances, progerin expression resulted in slight to moderate hyperplasia in the IFE (as judged by phospho-Histone 3 staining), hyperkeratosis, an accumulation of K5-positive cells within the suprabasal layer, disrupted maturation of sebaceous glands, impaired wound healing, increased inflammation and hair thinning. Keratinocytes derived from these mice exhibited an impaired ability to form colonies *in vitro,* accumulated γ-H2A-X foci, (indicative of unrepaired DNA damage), stained positive for senescence-associated β-galactosidase and secreted pro-inflammatory cytokines, collectively known as senescence-associated secretory phenotype (SASP).

In contrast to postnatal progerin expression, constitutive expression of progerin during murine embryonic development resulted in a more detrimental phenotype, including trans-epidermal water loss, dry scaly skin, impaired wound healing and death 2 weeks after birth. Further examination of these mice revealed that cells in the basal epidermis exhibited a shift from asymmetrical towards symmetrical cell division. This impaired polarity distorts epidermal homeostasis and results in stem cell exhaustion, as judged by a reduced number of CD34+/alpha6-integrin + epidermal stem cells [29].

The inducible system also permitted the authors to investigate whether the damage caused by transient exposure to progerin would be reversible. To achieve this, mice were exposed to progerin from postnatal day 0 onward and developed signs of skin aging, including hair thinning and skin crusting after 4 weeks. These phenotypes progressively became worse at 7 weeks, after which, progerin expression was turned off. At 13 and 20 weeks of age, i.e. 6 and 13 weeks post progerin removal, respectively, mice previously exposed to progerin appeared indistinguishable from their wild type counterparts: Histological examination of the skin revealed fewer areas of hair loss and epidermal hyperplasia, normal sebaceous glands, and marked reduction of immune cell infiltration [54]. These results suggest that an early intervention, even after the clinical characteristics of HGPS have manifested themselves, might be beneficial for HGPS patients. Lastly, systemic administration of telomere specific ASOs reduced telomere-associated DNA damage foci and DDR activation, restored epidermal homeostasis and skin development, reduced dermal inflammatory infiltration and led to an extension of their lifespan [39].

12. Conclusions

Since discovering the genetic basis for progeria, a multitude of different cellular and organismal model systems have been developed that contributed greatly to our understanding of how alterations in the nuclear lamina cause diseases. However, some key questions remain. On an organismal level, it is still unclear how mutations in lamin A and its processing specifically affect certain tissues, and how this in turn results in such a wide spectrum of complex disorders. Second, it remains puzzling how progerin expression results in such a large variety of cellular defects, and how they are mechanistically and causally linked. Third and possibly the most obvious question is what progeroid syndromes tell us about fundamental processes of normal human aging. A number of key phenotypes can be observed in progeria as well as during chronological aging; these include the loss of peripheral heterochromatin, the presence of DNA damage foci and DDR activation and an accumulation of senescent cells in aged tissues, including skin [55,56]. Several studies also suggested that lamin A

precursors accumulate in normally aged tissues, possibly due to *ZMPSTE24* downregulation or defective *LMNA* splicing [57].

Research in progeria has also led to the development of various proof of principle anti-aging strategies. These include morpholino- or CRISPR/Cas9-based approaches, small molecule inhibitors, modulation of signalling pathways including NF-κB and mTOR, as well as more general or sequence-specific blockage of DDR pathways [20,21,28,49–52]. Taken together, these rare genetic diseases have contributed greatly to our understanding of fundamental cell biology and the biology of aging. Thus, greater in-depth research into progeroid syndromes and other laminopathies is warranted and may provide opportunities to develop novel treatments for these devastating diseases.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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