Hutchinson-Gilford progeria syndrome as a model for vascular aging

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Abstract

Hutchinsion-Gilford progeria syndrome (HGPS) is a premature aging disorder caused by a *de novo* genetic mutation that leads to the accumulation of a splicing isoform of lamin A termed progerin. Progerin expression alters the organization of the nuclear lamina and chromatin. The life expectancy of HGPS patients is severely reduced due to critical cardiovascular defects. Progerin also accumulates in an age-dependent manner in the vascular cells of adults that do not carry genetic mutations associated with HGPS. The molecular mechanisms that lead to vascular dysfunction in HGPS may therefore also play a role in vascular aging. The vascular phenotypic and molecular changes observed in HGPS are strikingly similar to those seen with age, including increased senescence, altered mechanotransduction and stem cell exhaustion. This article discusses the similarities and differences between age-dependent and HGPS-related vascular aging to highlight the relevance of HGPS as a model for vascular aging. Induced pluripotent stem cells derived from HGPS patients are suggested as an attractive model to study vascular aging in order to develop novel approaches to treat cardiovascular disease.

Keywords: Hutchinson-Gilford progeria syndrome, induced pluripotent stem cells, mechanotransduction, senescence, stem cells, vascular aging.

Abbreviations

EC	Endothelial cell
ECM	Extracellular matrix
EPC	Endothelial progenitor cell
ESC	Embryonic stem cell
HGPS	Hutchinson-Gilford progeria syndrome
iPSC	Induced pluripotent stem cell
MSC	Mesenchymal stem cell
NF	Nuclear factor
NO	Nitric oxide
ROS	Reactive oxygen species
VSMC	Vascular smooth muscle cell

Introduction

It is widely accepted that the incidence of chronic disease is correlated with age. Age-related changes in vascular structure and function lead to elevated risks of developing cardiovascular disease. An improved understanding of the molecular basis of vascular aging could lead to the development of more targeted and effective treatments for cardiovascular disease. Models of accelerated aging provide a useful basis to facilitate the study of age-related vascular deterioration and thus represent an essential tool in the field of biogerontology. Several reviews have discussed the relevance of premature aging disorders to study age-related losses in cell and tissue function (Bellantuono et al. 2012; Burtner and Kennedy 2010; Serio 2011). The activation of 65 major cellular signalling pathways were compared between cells from young Hutchinson-Gilford progeria syndrome (HGPS) patients and cells from young, middle-aged and old healthy donors. The signalling in HGPS cells was more closely related to middle-aged and aged cells than their young counterparts. This study provided evidence that cellular aging is the precondition for organismal aging and that HGPS results in accelerated cellular aging. This review summarizes the similarities and differences between vascular aging and premature vascular aging in HGPS to better understand age-related alterations in the molecular and cellular architecture. The relevance of HGPS as a model for cardiovascular aging is discussed with respect to vascular phenotype, molecular signalling and stem cell function. Finally, this review also points towards the utilization of induced pluripotent stem cells (iPSCs) derived from HGPS patients as an effective model to study biological vascular aging.

Cardiovascular phenotype in HGPS and aging

Cardiovascular phenotype of aging

Age-related alterations in the vasculature result in a higher susceptibility to develop cardiovascular disease, even in seemingly healthy individuals. Vascular aging is associated with increased vascular stiffness and decreased vessel compliance (Sawabe 2010; Wang and Bennett 2012). Vascular remodeling is an important process of arterial aging consisting in intimal and medial thickening, luminal dilatation, reorganization of the extracellular matrix (ECM), as well as reduced elasticity. The decline in vessel elasticity with age is mostly due to increased collagen deposition and crosslinking, as well as fragmentation and degeneration of the elastic fibers. Increased vascular inflammation and altered intercellular communication also significantly contribute to vascular aging. Endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) undergo phenotypic and functional changes during aging, resulting in the increased secretion of proinflammatory molecules and in the decreased production of vasodilators (reviewed by Wang and Bennett 2012 and Wang *et al.* 2014). Aged VSMCs possess a greater migration capacity than their young counterparts. Together with the age-associated EC dysfunction, this migratory potential leads to the invasion of the subendothelial space by VSMCs, leading to further inflammation and vascular remodelling (Lee and Park 2013; Sawabe 2010). Conversely, decreased VSMC numbers are observed in the medial layer of the artery in part due to apoptosis, contributing to the general loss of arterial VSMCs with age. VSMC dysfunction is thought to be one of the major triggers of vascular calcification, a critical problem in vascular aging (Rennenberg et al. 2009). The inflammation, matrix deposition and calcification events associated with EC and VSMC dysfunction in turn increase the risk of cardiovascular events.

Molecular mechanism of HGPS

HGPS is a premature aging disorder with an occurrence rate of approximately 1 out of 4 million births worldwide (Hennekam 2006). Although few cases have been thoroughly documented, the clinical

presentation of most cases was similar. The typical clinical characteristics observed are growth retardation, skeletal muscle atrophy, pronounced atherosclerosis, decreased joint range of motion, failure to thrive, sclerodermatous skin changes, prominent eyes, alopecia, micrognathia, and decreased subcutaneous fat (Hennekam 2006; Merideth et al. 2008). Children with HGPS appear healthy at birth but their condition degrades after the first year of life. These patients usually succumb to the pathologies associated with HGPS in their teenage years, mostly due to cardiovascular complications.

HGPS is one of the most severe laminopathies, a group of diseases caused by a mutation in the LMNA gene coding for nuclear lamins. Lamins are type V intermediate filaments that are major components of the nuclear lamina. They play essential roles in supporting the structure and shape of the nucleus, in chromatin organisation, DNA repair, mitosis, gene transcription and cell differentiation (reviewed by Andres and Gonzalez 2008; Zuela et al. 2012). Prelamin A is the primary translational product of the lamin A mRNA. Prelamin A undergoes complex posttranslational modifications including farnesylation, methylation and several proteolytic processing events (Rusinol and Sinensky 2006). The last step of prelamin A processing consists in proteolytic cleavage by the zinc metalloproteinase Zmpste24, creating a mature unfarnesylated and unmethylated lamin A (Pendas et al. 2002).

The majority of HGPS cases are caused by a *de novo* silent heterozygous mutation at G608 in exon 11 of the LMNA gene, which codes for lamin A and C (De Sandre-Giovannoli et al. 2003; Eriksson et al. 2003). This mutation increases the probability of an internal deletion of 150 nucleotides due to the use of a cryptic splice site donor. This modification in lamin A splicing produces an isoform of lamin A called progerin which remains farnesylated due to the absence of a 50 amino acid sequence that contains the Zmpste24 proteolytic cleavage site. The hydrophobic properties of the farnesylated form of lamin A lead to its anchoring and accumulation at the nuclear envelope. Recent evidence provided by Kalinowski and colleagues (Kalinowski et al. 2014) suggests that progerin association to the nuclear membrane is also due to increased electrostatic interactions and aggregation. Even in its unfarnesylated form, progerin

forms aggregates at the membrane, underlining the importance of both the intrinsic toxicity of progerin and its farnesylated terminus. The progerin tail was found to be more compact and less heterogeneous than the wild-type lamin A tail, which is thought to alter the interactions between progerin and DNA or other proteins (Qin et al. 2011). The abnormal interactions between progerin (both its truncated tail and its farnesylated end) and the nuclear lamina as well as other nuclear components lead to alterations in nuclear shape, thickening of the lamina, loss of peripheral heterochromatin and changes in the organization of nuclear pore complexes (Goldman et al. 2004). The current therapeutic approach for HGPS mainly aims to reduce the incidence of complications of the disease. Current and upcoming clinical trials combine this approach with the administration of farnesyltransferase inhibitors (Table I).

Progerin and lamin A contribution to biological aging

Lamin A plays diverse and important structural and regulatory roles in nuclear scaffolding, nuclear pore formation, chromatin organization and gene regulation. Subtle differences in prelamin A processing or production can therefore result in critical changes including accelerated aging (Candelario et al. 2008). Candelario *et al.* showed that increased levels of wild-type lamin A lead to phenotypic changes similar to those observed in HGPS fibroblasts (Candelario et al. 2011). In addition, Zmpste24 was downregulated with age and in response to oxidative stress, supporting the hypothesis that defective prelamin A processing is involved in biological aging (Ragnauth et al. 2010). Several studies have pointed towards a role of progerin in healthy aging and vascular disease (McClintock et al. 2007; Olive et al. 2010; Rodriguez et al. 2009; Scaffidi and Misteli 2006). Progerin accumulates in an age-dependent manner in dermal fibroblasts as well as in the arteries of healthy patients (McClintock et al. 2007; Olive et al. 2010). Aged fibroblasts display nuclear defects similar to HGPS cells. The increased levels of progerin with age in non-HGPS individuals results in the accumulation of wild-type lamin A at the nuclear periphery

(Scaffidi and Misteli 2006). These observations suggest that the mechanisms that lead to aberrant nuclear morphology and chromatin disorganisation in HGPS may also affect aged cells. Notably, the cryptic splice donor site that produces progerin is activated in senescent cells (Cao et al. 2011). Telomere attrition results in the alternative splicing of several genes including progerin, thus presenting a complex and synergistic relationship between telomere shortening, progerin and senescence (Cao et al. 2011). This mechanism is telomere-dependent since telomerase reverse transcriptase-based cell immortalization resulted in the suppression of progerin production (Cao et al. 2011). In addition, the formation of insoluble progerin aggregates during mitosis caused aberrant chromosome segregation and binucleation (Cao et al. 2007). Similar mitotic defects were seen in wild-type late-passage fibroblasts expressing low levels of progerin (Cao et al. 2007). Moreover, the ectopic expression of progerin in tumor cells can lead to cell proliferation arrest associated with a multinucleated cell phenotype (Moiseeva et al. 2015). Together, these observations strongly suggest that progerin accumulation also impacts cell dysfunction and senescence in biological aging.

Similarities and differences between HGPS and aging phenotypes

Similar to elderly individuals, HGPS patients are prone to elevated arterial augmentation rate, decreased compliance and thickening of the adventitia (Merideth et al. 2008). HGPS patients also display an elevated platelet count and prolonged prothrombin times compared to age-matched individuals (Merideth et al. 2008). Calcification of the aortic valve and hypertrophy of the left ventricle are frequently observed. Olive and colleagues described the extensive adventitial fibrosis and the frequent atherosclerotic lesions present in the arterial histological sections of HGPS patients (Olive et al. 2010). Intimal lesions were mainly fibrotic and acellular, closely resembling atheromatous lesions in physiological aging. Significant VSMC depletion in the aortic media and thickening of the mitral valve were observed (Olive et al. 2010).

The autopsy of two patients of age 11 and 20 revealed a substantial decrease in VSMCs in the medial layer of the aorta (Stehbens et al. 1999). However, no clear venous VSMC depletion has been reported to date. Fibrous tissue displaying disorganised and non-circular arrangement of the fibers was observed in the medial layer of arteries instead of VSMCs. The main type of collagen observed in the intimal thickening was identified as type I, whereas collagen type IV showed pericellular distribution in the media, characteristic of the collagen distribution observed in atherosclerosis (Stehbens et al. 2001). Children suffering from HGPS displayed elevated carotid-femoral pulse wave velocity, abnormally echodense vascular walls, increased systolic and diastolic blood pressure, and decreased arterial compliance (Gerhard-Herman et al. 2012). The VSMCs that remained in the arteries were loosely dispersed with abnormal cell morphology. A concomitant increase in fibrotic tissue, proteoglycans and collagen was noted (Gerhard-Herman et al. 2012; Stehbens et al. 1999). In light of these observations, the HGPS vascular phenotype is likely caused by defective vascular remodeling with a progression very similar to physiological aging.

The characteristic phenotypic traits observed in HGPS patients have been reproduced to diverse extents in mouse models such as LMNA knockout mice, as well as mice carrying a specific homozygous or heterozygous mutation on the LMNA gene (G609G), or Zmpste24-deficient mice (Zhang et al. 2013). Of particular relevance for vascular aging is a mouse model carrying a G608G mutated human LMNA gene on a bacterial artificial chromosome that recapitulates most of the cardiovascular features seen in HGPS, including arterial calcification, severe VSMC depletion, ECM deposition, as well as adventitial and medial thickening (Varga et al. 2006). This mouse model also showed increased arterial hyaluronan content with age (Varga et al. 2006), which could represent an early event of atherogenesis. Indeed, hyaluronan accumulates in early atherosclerosis and regulates VSMC proliferation and migration (Evanko et al. 1999).

A recent study of a mouse model carrying a single silent mutation in the LMNA gene (G609G) showed important aortic calcification, together with increased expression of the osteogenic markers BMP-2 and Runx2 in VSMCs (Villa-Bellosta et al. 2013). Compared to wild-type controls, the VSMCs from mice carrying the G609G mutation had a decreased capacity to inhibit calcium phosphate deposition, impaired mitochondrial function and ATP production, as well as decreased levels of inorganic pyrophosphate (Villa-Bellosta et al. 2013). Consistent with this calcification mechanism, Csoka *et al.* showed that the expression of ectonucleotide pyrophosphatase 1, an enzyme that generates inorganic pyrophosphate and hence inhibits calcification, was significantly lower in HGPS fibroblasts compared to age matched controls (Csoka et al. 2004). The impaired capacity of VSMCs to inhibit calcification could partly be driven by a loss of contractility and eventually to a transition towards an osteoblastic phenotype. In calcified vessel walls, VSMCs tend to express bone or cartilage-associated markers such as Runx2, Sox9 and ALP (Shanahan 2013). Following this osteoblastic differentiation, the VSMCs start to secrete matrix vesicles that contribute to calcification by creating hydroxyapatite nucleation sites. Interestingly, undifferentiated progeric mesenchymal stem cells (MSCs) express high levels of osteopontin, an osteogenic marker, and exhibit functional characteristics associated with osteogenic differentiation such as calcium deposition (Scaffidi and Misteli 2008). The differentiation of mesenchymal lineages towards osteogenic cells suggests a direct link between the expression of progerin and calcification via functional changes in the VSMC phenotype. In normal vascular aging, VSMC senescence also leads to increased Runx2 and ALP expression (Nakano-Kurimoto et al. 2009). Liu and colleagues demonstrated that prelamin A accumulates *in vitro* and *in vivo* in calcifying VSMCs in age-related vascular calcification (Liu et al. 2013). Prelamin A accumulation in pre-senescent VSMCs may promote DNA damage and osteogenic differentiation, suggesting a direct role for lamin A processing in vascular calcification both in HGPS and in biological aging.

Vascular inflammation and EC dysfunction actively contribute to blood vessel aging and atherosclerosis. Inflammatory mechanisms could explain the high prevalence of atherosclerotic lesions in HGPS. Bonello-Palot and colleagues demonstrated that intercellular adhesion molecule 1 was elevated in ECs expressing prelamin A (Bonello-Palot et al. 2014). Prelamin A expression led to increased monocyte adhesion, a feature thought to contribute to the initiation of atherosclerosis. A comparative study of two mouse models of accelerated aging (Zmpste24-deficient and LMNA G609G) demonstrated that both prelamin A and progerin accumulation at the nuclear envelope results in increased nuclear factor (NF)-κB activation and systemic inflammation (Osorio et al. 2012). Increased levels of NF-κB activation were previously observed in normal and accelerated models of aging. Together, these studies suggest that the NF-κB pathway plays a critical role in premature vascular aging (Osorio et al. 2012). In summary, the HGPS cardiovascular phenotype significantly overlaps with several features associated with typical vascular aging and atherosclerosis (Table 2). Initially, patients with HGPS do not display any cardiovascular abnormalities as reported by sonography and electrocardiography (Hennekam 2006). However, vascular function decreases over time, leading to calcification, inflammation, plaque erosion and ECM deposition - all of which are hallmarks of atherosclerosis and vascular aging (Olive et al. 2010).

Mechanisms contributing to vascular dysfunction in HGPS and aging

Telomere shortening

Several lines of evidence suggest an important relationship between senescence in aging and age-associated disease, particularly in atherosclerosis where the accumulation of senescent cells is correlated with the severity of the vascular lesion. Increased numbers of senescent cells were quantified in atherosclerotic plaques by several studies (Chang and Harley 1995; Matthews et al. 2006; Vasile et al.

2001). Senescent ECs from atherosclerotic patients are characterized by low EC growth potential, specific changes in cell phenotype, gene and protein expression and telomere shortening (Voghel et al. 2007). The resulting EC dysfunction likely reduces the EC contribution to atheroprotection and vascular repair. Oxidative stress was identified as an important cause for telomere shortening in ECs (Kurz et al. 2004) and in endothelial progenitor cells (EPCs) (Satoh et al. 2008). Telomere loss was more important in regions of the vasculature with greater levels of hemodynamic stress, which are more susceptible to atherosclerosis (Chang and Harley 1995). Consistent with these results, Okuda *et al.* demonstrated that there is a higher rate of telomere shortening in the distal abdominal aorta than in the proximal abdominal aorta (Okuda et al. 2000). It was hypothesized that higher shear stress results in higher cell turnover and, consequently, in increased telomere attrition. Another possibility is that shear stress hyperactivates the mitogen-activated protein kinase pathway (Esue et al. 2006), which can cause senescence (Deschenes-Simard et al. 2013). Inhibition of this pathway can rejuvenate human cells and increase life span in flies (Deschenes-Simard et al. 2013; Slack et al. 2015). EC proliferative arrest due to senescence could then lead to impaired endothelial function including defective vascular healing, thus increasing the risk for atherosclerosis.

Similar to aged cells, enhanced telomere erosion was observed in progerin-expressing cells (Decker et al. 2009; Huang et al. 2008). Telomere shortening in HGPS cells could result from increased cell replication due to a high cell turnover rate or from increased telomeric DNA damage together with altered DNA repair responses, or both. The latter mechanism is supported by accumulating experimental evidence. Indeed, telomeres display an increased binding affinity for lamina proteins in cells expressing mutant forms of lamin A, resulting in telomere aggregates enriched in phosphorylated histone H2AX, a DNA damage marker (Raz et al. 2008). The presence of progerin led to DNA damage targeted specifically to the telomeres, promoting telomere dysfunction and chromosomal aberrations (Benson et al. 2010). These effects were counter-acted by the presence of telomerase. In addition, HGPS cells

display significantly reduced telomere mobility, possibly due to the alteration of the internal topography of the nucleus by progerin (De Vos et al. 2010). This finding was surprising, as telomere shortening typically leads to increased telomere mobility, which may act to increase the probability of encountering telomeric repair or elongation enzymes. Telomerase deficient mice and patients suffering from various premature aging syndromes are all characterized by increased genomic instability, suggesting that short telomeres enhance aging as a result of increased DNA damage (Blasco 2005).

Oxidative stress and DNA damage

Premature senescence has been observed in HGPS fibroblasts (Huang et al. 2005; Huang et al. 2008). Senescence can be induced by external stimuli such as oxidative stress, DNA damage and oncogenes, which activate the senescence cascade prematurely and independently of telomere length, as reviewed by Fyhrquist *et al.* (2013).

Oxidative stress can induce senescence via telomere-independent mechanisms by causing direct damage to genomic and mitochondrial DNA. Voghel *et al.* showed that oxidative stress prevents the telomerase-dependent immortalization of ECs (Voghel et al. 2007). Oxidative stress and DNA repair control mechanisms are likely essential in preventing cell senescence, particularly in the pro-oxidative environment of atherosclerotic regions. HGPS and aged wild-type fibroblasts exhibited increased levels of reactive oxygen species (ROS) and protein oxidation, as well as decreased proteasome activity (Miyoshi et al. 2006; Viteri et al. 2010). Datta *et al.* proposed that oxidative stress induced by progerin results in important perturbations of the Ran protein distribution (Datta et al. 2014). Ran is a G protein of the RAS family involved in nuclear transport during interphase, as well as mitotic spindle assembly and nuclear envelope reassembly during mitosis. The altered Ran gradient between the nucleus and the cytoplasm may thus impair nucleocytoplasmic transport and other Ran-mediated processes in progeric

cells. Synergistic effects between ROS production, the structure of the nuclear lamina and the disruption of the Ran system may eventually lead to altered import and export of high molecular weight proteins in HGPS (Datta et al. 2014; Snow et al. 2013).

DNA damage triggers a transient growth arrest via the activation of the p53 pathway in order to allow DNA repair prior to cell division. However, similar to the telomere erosion cascade, cells enter permanent proliferation arrest if DNA damage is too extensive. The level of DNA damage in somatic and germ cells is correlated with age in murine models (Sedelnikova et al. 2004). The accumulation of non-repairable DNA is thought to contribute to organismal aging (Sedelnikova et al. 2004). A recent study found that mislocation of xeroderma pigmentous group A, a nucleotide excision repair protein, was associated with the faulty repair of double-stranded breaks in progeric cells, probably by preventing the access of DNA repair factors to these sites and delaying DNA repair (Liu et al. 2008). Cells approaching senescence and aged cells also display delayed double-stranded DNA break repair, resulting in the accumulation of DNA damage with age (Sedelnikova et al. 2008). The role of nuclear abnormalities in DNA repair remains unclear, since farnesyltransferase inhibitors that rescued the abnormal shape of the nuclei failed to reduce the level of DNA damage in HGPS fibroblasts (Liu et al. 2006). Changes in epigenetic modifications and DNA repair have been reviewed in the context of normal aging (Wu and Roks 2014) as well as for HGPS (Arancio et al. 2014).

It was previously shown that p53 target genes are upregulated in HGPS, and that the inactivation of p53 could rescue the early proliferative defects generally seen in HGPS cells (Kudlow et al. 2008; Varela et al. 2005). As nuclear lamins play an important role in the regulation of the p53 pathway, it is not surprising that impaired processing of prelamin A affects p53 signalling. Zmpste24-deficient mice have impaired p53 signalling, promoting senescence and possibly contributing to accelerated aging (Varela et al. 2005). Liu *et al.* observed increased DNA damage, defective DNA repair and genomic instability in fibroblasts from Zmpste24-deficient mice or HGPS patients (Liu et al. 2005). Their findings

support the hypothesis that lamin A plays an important role in maintaining genome integrity via the recruitment of DNA damage and response proteins (Liu et al. 2005). An impaired recruitment of p53 binding protein 1 and Rad51 was observed in HGPS and Zmpste24-deficient fibroblasts, resulting in defective DNA repair (Liu et al. 2005).

Biomechanical stress and mechanotransduction in HGPS and aging

Shear stress

It is now widely accepted that cells can transduce mechanical stimuli into biochemical signalling – a process termed mechanotransduction – and that incorrect response to these stimuli can impair cellular and tissue homeostasis. The response of vascular cells to flow patterns and shear stress progressively change with age. ECs sense and distinguish different types of flow (laminar or turbulent, reversing or non-reversing, pulsatile or continuous) and react accordingly (Helmlinger et al. 1991). ECs exposed to low oscillatory flow assume a more rounded morphology, which is characteristic of an increased permeability to plasma constituents, cell turnover rate and intimal penetration (Helmlinger et al. 1991). Regions with disturbed blood flow and high shear stress are more prone to atherosclerosis (Bond et al. 2011; Chang and Harley 1995; Frangos et al. 1999; Rouleau et al. 2010) . Flow angle relative to cytoskeletal axis severely affected the activation of endothelial NO synthase and the proinflammatory transcription factor NF-κB. Together, these observations suggest that disturbed flow enhances local inflammation (Wang et al. 2013).

Shear stress causes up-regulation of NO in young but not old ECs (Hoffmann et al. 2001). NO up-regulation is atheroprotective and reduces senescence. Therefore, aging is a risk factor for

atherosclerosis due to, amongst others, decreased NO production (Hayashi et al. 2006). Differences in gene expression between young and senescent ECs were also observed in response to changes in the level of laminar wall shear stress (Mun et al. 2009). Overall, impaired mechanotransduction and decreased sensitivity to shear stress associated with aging can lead to cell senescence and increased risk of developing cardiovascular disease.

HGPS skin fibroblasts exhibit increased mechanosensitivity and apoptosis under biomechanical strain (Verstraeten et al. 2008). HGPS VSMCs are unusually sensitive to ischemic and hemodynamic stress, leading to severe arterial VSMC depletion, which likely promotes HGPS-associated atherosclerosis (Stehbens et al. 1999). The nuclear defects seen in progeric vascular cells are potentially responsible for their altered mechanical response to shear stress. The increased nuclear fragility of LMNA-deficient cells is correlated with impaired transcriptional activation responses, including aberrant responses to NF-κB signalling (Lammerding et al. 2004). Normally, nuclei exposed to shear stress up-regulate and redistribute A-type lamins within the nucleus (Philip and Dahl 2008), which minimizes the total force exerted on the nucleus (Hazel and Pedley 2000). The nuclear lamina in progeric fibroblasts has a decreased ability to rearrange under mechanical stress, which may explain the significantly reduced shear stress adaptation capacity of cell lines overexpressing progerin (Dahl et al. 2006; Philip and Dahl 2008). The shear stress response of wild-type HeLa cells was attenuated when they were placed in mixed culture with HeLa cells overexpressing progerin (Philip and Dahl 2008). Small fractions of cells expressing mutant lamin A may thus significantly alter the general response to shear stress in vascular tissues, reducing the overall atheroprotective potential of the ECs and contributing to age-associated cardiovascular disease (Philip and Dahl 2008).

The altered responses of aged or progeric vascular cells to mechanical stimuli were also linked to changes in cell structure, in particular intermediate filament and cytoskeletal structure. Increased expression levels of cytoskeletal proteins such as α-actin, α-tubulin and vimentin were observed in HGPS

fibroblasts compared to controls (Wang et al. 2012). Senescent fibroblasts were also characterized by long and dense vimentin networks (Nishio and Inoue 2005). Since vimentin strongly interacts with actin, altered vimentin expression is directly related to changes in cell stiffness (Esue et al. 2006). In the ascending aorta of G608G LMNA mutant mice, Song *et al.* observed a reduced expression of many proteins involved in mechanotransduction or cytoskeletal organization, as well as an elevated expression of many mitochondrial enzymes and ECM proteins (Song et al. 2014). Compared to wild-type controls, vimentin and other type III filaments protein levels were reduced in VSMCs, but increased in ECs when the cells were exposed to high hemodynamic shear stress *ex vivo* (Song et al. 2014). Vimentin-deficient fibroblasts were shown to be less mechanically stable and significantly less stiff than wild-type controls (Eckes et al. 1998). Consequently, the elevated level of vimentin in ECs could potentially increase EC resistance to shear stress via cytoskeletal stiffening, explaining why the endothelium is generally well-preserved in biopsies of HGPS vessels. In contrast, the impaired mechanotransduction and increased fragility of the cytoskeleton observed in VSCMs could precede the vasculopathy and VSMC depletion observed in HGPS.

Extracellular matrix changes and cell migration

Tissue cohesion and mechanical homeostasis are regulated by cell-matrix interactions. The ECM substrate stiffness alters the mechanical strain exerted on cells, which influences cell morphology and differentiation (Humphrey et al. 2014). On the other hand, cells regulate ECM composition and degradation in response to these cues and maintain fundamental ECM mechanical and biological properties.

Vascular ECM remodeling with age results in increased ECM stiffness and altered ECM-cell interactions. In both aged mice and progeric mice, the excessive expression of collagen VI can lead to

increased arterial stiffness (de Castro Bras et al. 2014; Song et al. 2014). In a gene expression study of HGPS fibroblasts, Csoka *et al.* demonstrated that, after transcription factors, the genes most profoundly affected by HGPS were ECM components (Csoka et al. 2004). HGPS fibroblasts displayed elevated expression of ECM proteins and decreased expression of ECM remodelling enzymes such as matrix metalloproteinases, which could lead to excessive ECM deposition (Harten et al. 2011). Another possible explanation for the changes in ECM organization observed in progeric tissues is the inhibition of the Wnt signalling pathway by mutant lamin A, resulting in altered ECM synthesis (Hernandez et al. 2010). Together, changes in the ECM composition and remodelling can lead to increased vascular stiffness and altered mechanotransduction both in HGPS and aged blood vessels.

Cell invasion and migration are required for adequate wound healing and vascular development. The higher ECM deposition and nuclear stiffness observed in aged and progeric blood vessels may result in slower cell migration through the 3D matrix (Booth-Gauthier et al. 2013). The increased nuclear stiffness of HGPS cells compared to controls prevents the nuclear deformation that facilitates cell migration through tight spaces. Together with reduced force generation, this increased nuclear stiffness may explain the reduced motility of progeric cells (Booth-Gauthier et al. 2013). Supporting this idea, Ribeiro *et al.* observed that melanoma cells overexpressing progerin also displayed reduced migratory responses, which could account for the reduced potential of metastatic cancer migration in HGPS patients (Ribeiro et al. 2014). The age-dependent accumulation of progerin in normal aging could be part of the mechanisms that play an important role in preventing malignant cell transformation, together with telomere shortening and senescence.

The role of stem cells in HGPS and aging

The effect of aging on stem cell function

Stem cells and progenitor cells play a critical role in tissue repair and maintenance, continuously replenishing terminally differentiated cells to cope with high cell turnover and injury. The age-related decline in the regenerative capacity of adult stem cells plays a key role in biological aging. Due to their long history of self-replication and differentiation, stem cells that accumulate mutations or DNA damage may initiate cancers. The accumulation of genomic damage and telomere erosion influences stem cell fate decisions, which can result either in dysfunction, malignant transformation, senescence or apoptosis (Sharpless and DePinho 2007). This precancerous progression is generally prevented by tumor suppressor mechanisms such as senescence and apoptosis. While protecting the organism from cancer, tumor suppressor pathways could cause stem cell exhaustion and eventually lead to defective tissue repair and maintenance, thus contributing to the aging phenotype. Adult stem cells are subjected to replicative and stress-induced premature senescence enhanced by ROS, DNA damage and telomere attrition (reviewed by Rossi et al. 2008). Moreover, a striking age-dependent decrease in telomere length was observed in several mouse stem cell compartments, such as the skin, small intestine, cornea, testis and brain (Flores et al. 2008). Consequently, stem cell exhaustion and dysfunction affect tissue homeostasis and contribute to the aging phenotype.

Stem cell exhaustion and dysfunction in HGPS

It was long thought that embryonic stem cells (ESCs) did not express lamin A/C until they begin to differentiate. However, mouse ESC were later shown to express low levels of lamin A/C mRNA and protein (Eckersley-Maslin et al. 2013). Multipotent skin-derived precursors also express progerin *in vivo*, suggesting that adult stem cells may be affected by progerin, similar to terminally differentiated cells (Wenzel et al. 2012). Figure 1 illustrates the progerin expression levels documented in a variety of

vascular and other mesoderm-derived cell lineages. A-type lamins transduce signals from the cytoskeleton to the nucleus and influence adult stem cell maintenance, differentiation and stress responses via different critical pathways, including the p53/p21, Notch, Wnt and NF-kB pathways. Lamin A mutations could therefore lead to a decreased protection against chronic stress in adult stem cells (Pekovic and Hutchison 2008). The proliferative potential of epidermal stem cells is severely decreased in Zmpste24-deficient mice (Espada et al. 2008). In these mice, the abnormal epidermal stem cell nuclear morphology and the subsequent chromatin disorganization result in the inactivation of several signaling pathways that control stem cell fate decisions such as the Wnt pathway (Espada et al. 2008).

A-type lamins and progerin are upregulated during pluripotent stem cell differentiation (Constantinescu et al. 2006). In mesoderm-derived lineages, progerin expression is generally higher in terminally differentiated cells than progenitor or stem cells (Figure 1). The increasing level of progerin expression during differentiation may alter stem cell fate decisions, especially during later developmental stages. Scaffidi and Misteli observed an abnormal tendency of progerin-expressing cells to differentiate spontaneously (Scaffidi and Misteli 2008). Interestingly, they demonstrated that Notch signalling, which is critical for stem cell differentiation and maintenance (Chiba 2006), was activated in HGPS fibroblasts, as well as wild-type mesenchymal stem cells carrying a progerin expression vector (Scaffidi and Misteli 2008).

The exhaustion, dysfunction or altered differentiation potential of vascular stem cells and progenitor cells could severely decrease the regeneration potential of vascular tissues with age or in HGPS. Tissues subjected to persistent mechanical stress or continuous growth may be more heavily affected in HGPS due to the high demand for regeneration and repair placed on the stem cell pool (Halaschek-Wiener and Brooks-Wilson 2007). The exhaustion of specific stem cells such as adipose-derived stem cells and hair follicle stem cells could explain many features of HGPS such as lipodystrophy

and alopecia. Corroborating this hypothesis, a decreased epidermal stem cell pool was observed in in transgenic mice carrying the common HGPS mutation, which was correlated with impaired wound healing (Rosengardten et al. 2011).

Vascular homeostasis in the context of stem/progenitor cell aging

Of particular relevance to cardiovascular aging are stem cell and progenitor cell populations involved in vascular homeostatis, such as EPCs, hematopoietic stem cells and MSCs (Figure 1). The contribution of these stem cell types to HGPS is summarized in Table 3, and their role in normal aging has been expertly reviewed elsewhere (Geiger et al. 2014; Minamino and Komuro 2008; Sharpless and DePinho 2007; Stochaj et al. 2013). Compared to young donors, MSCs from old donors are less proliferative, display reduced colony-forming capacity, increased DNA damage, decreased telomerase activity and increased apoptosis (Stochaj et al. 2013).

A-type lamins regulate MSC maintenance and regeneration. Consequently, MSCs and mesenchymal tissues are predominantly affected in HGPS. Pachecho *et al.* used a subpopulation of bone marrow stromal cells transduced with a GFP-progerin fusion protein to assess the role of progerin expression in stem cell dysfunction (Pacheco et al. 2014). Altered expression and localization of proteins crucial to stem cell self-renewal such as Notch2 and Oct4 were observed. Moreover, cytoplasmic and nuclear stiffness increased, while cell proliferation and migration decreased. MSC function was impaired at progerin concentrations similar to the levels present in MSCs from aged donors. The expression of progerin also reduced the adipogenic differentiation potential of MSCs from HGPS patients, which could partially explain the loss of subcutaneous adipose tissue in HGPS patients (Scaffidi and Misteli 2008). Notably, decreased adipogenic potential was reported in a study using adipose tissue-derived aged MSCs

(Alt et al. 2012). Together, these studies indicate that progerin accumulation may directly affect MSC function and MSC contribution to vascular repair.

EPCs are thought to contribute to vascular repair and regeneration. The regenerative capacity of EPCs may be impaired during aging as well as in patients with cardiovascular diseases such as coronary artery disease and aortic valve stenosis (Matsumoto et al. 2009; Vasa et al. 2001). EPC proliferation, chemotaxis, recruitment to sites of vascular injury and survival *in vitro* decline with age (Chang et al. 2007; Heiss et al. 2005). The expression of farnesylated prelamin A in EPCs resulted in cell senescence as well as decreased angiogenic properties (Bonello-Palot et al. 2014). Both aging and progerin accumulation may significantly impair vascular homeostasis via EPC exhaustion and dysfunction.

iPSCs from HGPS donors as a model for vascular aging

Due to the small number of HGPS patients and the difficult access to vascular biopsies, studying the human HGPS vascular phenotype is challenging. Until recently, studies of HGPS progression relied on primary culture of HGPS donor cells, ectopic expression of lamin A or progerin in human cell lines or primary cells, or *in vivo* studies of HGPS rodent models. A powerful emerging model to study human development and aging is the use of iPSCs. Established iPSC lines from patients suffering from genetic diseases can theoretically be differentiated into any cell type in the human body. The differentiated cells could then be used to probe the mechanisms leading to abnormal cell function or development, as well as for drug screens. In 2011, the generation of iPSC lines from HGPS patients was reported by three independent groups (Ho et al. 2011; Liu et al. 2011; Zhang et al. 2011) using the four original reprogramming factors described by Takahashi and Yamanaka (Takahashi and Yamanaka 2006). Interestingly, the reprogrammed pluripotent cells lost HGPS defects such as abnormal nuclear architecture, progerin expression, as well as altered epigenetic modifications and gene expression

patterns (Liu et al. 2011; Zhang et al. 2011). However, the reprogramming efficiency of HGPS skin-derived fibroblasts was significantly lower than controls (Zhang et al. 2011) and late passage HGPS fibroblasts did not generate iPSCs (Liu et al. 2011). Zuo *et al.* (2012) examined this issue and found a negative correlation between the level of lamin A expression and reprogramming efficiency (Zuo et al. 2012). These results suggest that the changes in nuclear scaffolding caused by progerin interfere with the pluripotency gene expression cascade or the chromatin remodeling events required for cellular reprogramming.

Upon serum-induced HGPS-iPSC differentiation, lamin A and progerin expression was upregulated. Similar to primary fibroblasts from HGPS donor tissues, increased DNA damage and expression of senescence-associated markers, mislocalization of the nuclear protein LAP2, as well as nuclear aberrations were observed (Liu et al. 2011; Zhang et al. 2011). Zhang and colleagues successfully differentiated HGPS-iPSCs into mesenchymal stem cells, VSMCs, fibroblasts, ECs and neuronal progenitors, listed in descending order of progerin expression. The relative progerin expression levels measured in these lineages were consistent with the observation that HGPS mainly affects tissues of mesenchymal origin, while neurodegeneration is generally absent in HGPS patients. HGPS-iPSC-differentiated VSMCs and MSCs were severely affected by progerin and were hypersensitive to stress such as hypoxia and serum deprivation (Zhang et al. 2011). In a model of vascular regeneration after induced hindlimb ischemia in mice, the administration of MSCs derived from HGPS-iPSCs led to slower recovery rates than MSCs derived from wild-type iPSCs. This observation was associated with increased MSC death and senescence, suggesting that the hypersensitivity to hypoxic stress caused by progerin may contribute to the exhaustion of the MSC pool in HGPS (Zhang et al. 2011).

New knowledge on HGPS progression and on the molecular basis of the disease has already emerged from iPSC models. For instance, progerin accumulation was shown to downregulate DNA-dependent protein kinase catalytic subunit expression, which leads to a loss of VSMC proliferative

potential. This downregulation also progressively occurred in aged fibroblasts from normal donors, suggesting that this kinase subunit could serve as a novel cell senescence marker (Liu et al. 2011). Increased mechanosensitivity was observed in endothelial cells derived from HGPS-iPSCs, which may be due to elevated transient receptor potential cation channel V2 expression upon mechanical stimulation, causing Ca^{2+} overload and apoptosis (Lo et al. 2014). Moreover, Zhang *et al.* demonstrated that poly(ADP-ribose) polymerase 1 was severely downregulated in VSMCs derived from HGPS-iPSCs, resulting in reduced cell proliferation rates. Poly(ADP-ribose) polymerase 1 downregulation enhanced the activation of the non-homologous end joining pathway, leading to chromosomal aberration and cell death due to mitotic catastrophe (Zhang et al. 2014). This mechanism could explain the extensive VSMC loss in progeria patients and progeroid syndrome mouse models.

The iPSC technology constitutes a powerful platform for comparative and standardized drug screening or testing. Blondel and colleagues used HGPS-iPSCs to compare the 3 currently relevant treatments for HGPS: rapamycin, farnesyltransferase inhibitor and the combination of a statin and an aminobiphosphonate (Blondel et al. 2014). Their study revealed differences in prelamin A processing, as well as cell proliferation and osteogenic differentiation that may impact the therapeutic potential of these treatments. The iPSC technology offers the possibility of engineering organoids combining several cell types to study the effects of progerin accumulation on cell-cell interaction, and even tissue or organ function. The creation of iPSC banks from HGPS donors should significantly accelerate efforts to develop novel therapeutic approaches to treat progeroid syndroms or improve the quality of life during aging.

Conclusion

In HGPS patients, progerin expression leads to severe vascular complications. Studying the molecular mechanisms that link progerin accumulation to vascular cell dysfunction could lead to novel therapeutic approaches to improve the quality of life of HGPS patients. Progerin also accumulates in the vascular cells of healthy adults in an age-dependent manner. Progerin-expressing cells prematurely enter senescence and display alterations in paracrine and intracellular signalling. These changes result in systemic inflammation and increased risk of developing vascular defects such as atherosclerosis due to increasing arterial stiffness, systolic and pulse pressure as well as calcification. The accumulation of progerin at the nuclear membrane alters nuclear organisation and function, accelerates telomere attrition, increases DNA damage, and alters cellular responses to mechanical stimuli. HGPS shows most, if not all of the characteristic hallmarks of aging (Lopez-Otin et al. 2013). HGPS-associated aging provides a complementary approach to augment currently available model systems to study vascular aging and cardiovascular disease in the absence of traditional risk factors influencing aging such as low density lipoprotein cholesterol levels, hypertension and obesity. At present, the iPSC technology is poised to become indispensable for investigating both fundamental questions in aging research as well as for developing novel therapeutic options for HGPS patients. In summary, HGPS represents an effective and relevant model to deconstruct the biological complexity of vascular aging at the molecular and cellular level.

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Tables and figures

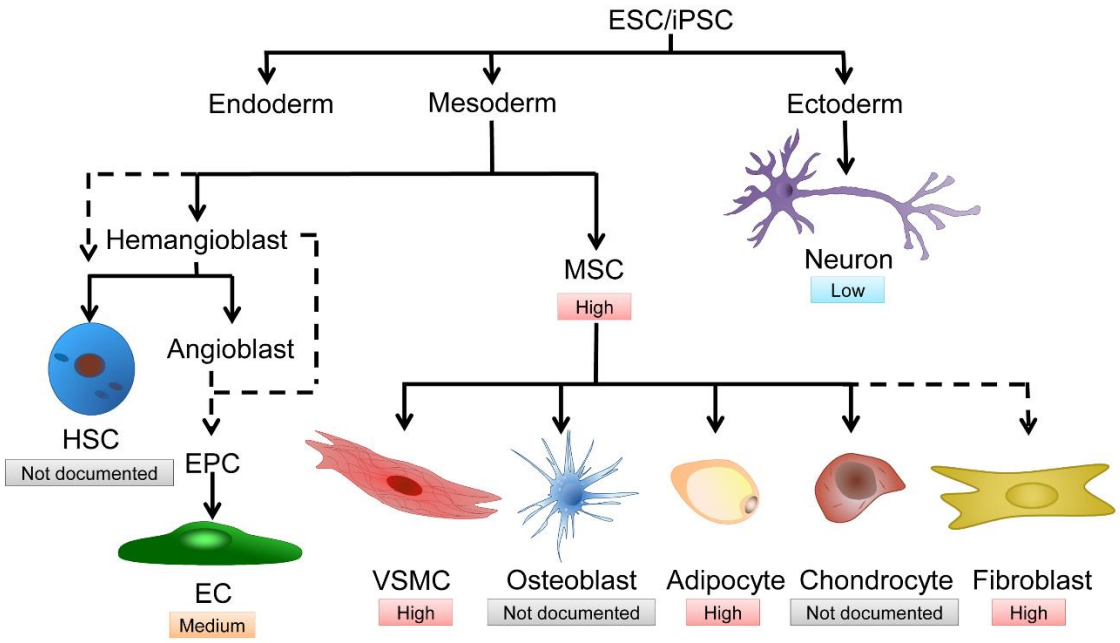

Figure 1. Developmental origin and progerin expression level of vascular cells relative to other lineages

Table 1. Past and upcoming clinical trial related to HGPS

No.	Study No.	Title	Sponsor	Intervention	Study Objective	Treatment duration	Phase	Status	Reference(s)
1	NCT00916747	Study of Zoledronic Acid, Pravastatin, and Lonafarnib for Patients With Progeria	Children's Hospital Boston	Drug: Lonafarnib, Zoledronic Acid, and Pravastatin	This study evaluates the combination of pravastatin (a statin), lonafarnib (a farnesyltransferase inhibitor) and zoledronic acid (a bisphosphonate that inhibits bone resorption) to prevent preprogerin farnesylation.	2 years	Phase II	Recruiting	Gordon et al., Circulation 2014
2	NCT00879034	A Study of Zoledronic Acid, Pravastatin, and Lonafarnib for Patients With Progeria	Children's Hospital Boston	Drug: Lonafarnib; Zoledronic Acid; Pravastatin	A combination of two oral agents (pravastatin and lonafarnib) and one intravenous (IV) agent (zoledronic acid) were administered at doses and schedule currently applied in pediatrics in order to inhibit farnesylation of abnormal lamin.	4 weeks - 6 months	Phase II	Completed	Gordon et al., Circulation 2014
3	NCT00094393	Clinical Studies of Progeria	National Human Genome Research Institute (NHGRI)	Observation	This study examined which body systems are affected in progeria patients and how each system is affected over time in order to try to develop new treatments.	5- to 10-year study	Observational study	Completed	DeBusk, J Pediat 1972; Pesce Clin. Dermatol. 1996; Badame Arch Dermatol, 1989; Merideth N Eng J Med 2008
4	NCT00425607	Phase II Trial of Lonafarnib (a Farnesyltransferase Inhibitor) for Progeria	Children's Hospital Boston	Drug: Lonafarnib	The goal of this study is to evaluate the therapeutic effect of oral lonafarnib in patients with HGPS.	2 years	Phase II	Unknown	Gordon et al., Circulation 2014, Gerhard-Herman, Hypertension 2012
5	NCT00731016	Treatment of the Hutchinson-Gilford Progeria Syndrome With a Combination of Pravastatin and Zoledronic Acid	Assistance Publique Hopitaux De Marseille	Drug: Zoledronic acid, pravastatin	Two molecules (zoledronic acid and pravastatin) were administered to evaluate their tolerance and efficacy in combination with the patient's weight, height and bone metabolism in Progeria treatment.	4 years	Phase II	Completed	Not Provided

Table 2. Phenotypic similarities and differences between HGPS and vascular aging

Phenotypic properties	Aging	HGPS	References
Arterial stiffness	↗	↗	(Lee and Park 2013; Merideth et al. 2008; Sawabe 2010)
Medial VSMC number	↘	↘↘	(Lee and Park 2013; Stehbens et al. 1999)
Expression of proinflammatory molecules	↗	↗	(Osorio et al. 2012; Wang and Bennett 2012)
Risk of atherosclerosis	↗	↗	(Olive et al. 2010; Wang and Bennett 2012)
ECM deposition	↗	↗	(Gerhard-Herman et al. 2012; Olive et al. 2010; Sawabe 2010)
Calcification	↗	↗	(Villa-Bellosta et al. 2013)
Systolic and pulse pressure	↗	↗	(Gerhard-Herman et al. 2012; Merideth et al. 2008)
Platelets count	-	↗	(Merideth et al. 2008)
Prothrombin time	-	↗	(Merideth et al. 2008)

Table 3. Main cellular dysfunction contributing to HGPS

Cell type	Main dysfunction in HGPS	Main effect of progerin or prelamin A accumulation	References
MSC	Altered differentiation potential Decreased cell proliferation and migration Hypersensibility to hypoxia	Loss of adipose tissue Decreased repair potential MSC exhaustion	(Scaffidi and Misteli 2008) (Pacheco et al. 2014) (Zhang et al. 2011)
EPC	Activation and progression of senescence and decreased angiogenic potential	Decreased repair potential	(Bonello-Palot et al. 2014)
EC	Impaired response to shear stress (↗ ICAM-1, ↘ eNOS activity) Increased nuclear and cytoskeleton stiffness	Vascular inflammation and atherogenesis	(Minamino et al. 2002) (Song et al. 2014)
VSMC	Increased sensitivity to hemodynamic stress Decreased capacity to inhibit calcium phosphate de position	VSMC depletion Increased calcification	(Stehbens et al. 1999) (Villa-Bellosta et al. 2013)
Fibroblast	Increased expression of ECM proteins Decreased expression of ECM remodelling enzymes	Increased ECM deposition and arterial stiffness	(Csoka et al. 2004) (Harten et al. 2011)

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