Hutchinson-Gilford Progeria Syndrome and its Relevance to Cardiovascular Diseases and Normal Aging

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Hutchinson-Gilford progeria syndrome (HGPS, OMIM 176 670) is an extremely rare, sporadic genetic syndrome with a reported prevalence of one in 4-8 million children worldwide. At April 2012, the total number of known living children with HGPS was 89 worldwide, according to data from the Progeria Research Foundation.

HGPS is classified as segmental premature aging with widespread phenotypic features resembling severe premature aging. Children with HGPS generally appear healthy at birth but display distinctive clinical features from the first years of life[1]. The major typical symptoms include severe growth retardation, hair loss, scleroderma-like skin, diminished subcutaneous fat, prominent eyes, prominent scalp veins, absent sexual maturation, reduced bone density, joint contracture, and premature atherosclerosis[2]. The cardiovascular diseases are the most serious aspect, because individuals with HGPS generally die at an average age of 11-13 years due to myocardial infarction (MI), heart failure or cerebrovascular accident caused by progressive atherosclerotic disease[1,3].

HGPS is believed to share some common mechanism with normal aging and geriatric cardiovascular disease. Thus, the pathogenesis and treatment of HGPS are receiving increasing attention, not only because the disease is distressing for affected children and their families, but also because it may offer researchers a rare opportunity to obtain insights into the mechanisms of natural aging, especially with respect to cardiovascular diseases. Here, we review the phenotype and pathogenesis of this fatal syndrome and introduce its relationship with physiological aging and geriatric cardiovascular diseases.

1. PHENOTYPE OF THE CARDIOVASCULAR SYSTEM

1.1 Clinical Features of the HGPS Cardiovascular System

The principal factor affecting mortality in HGPS individuals is cardiovascular disease (75%). Patients do not have any cardiovascular problems clinically in the first 5 years[3-5], but most gradually develop shortness of breath with exertion and easy fatigability from the age of 6-8 years. In the end phase, dyspnea can be extreme.

Other arteries may also be involved. Strokes have been reported at 4-19 years of age (average age 9 years)[3]. Cerebral infarction can result in seizures, hemiplegia, dysarthria and facial palsy, can follow a more protracted course with episodes of headache, dizziness and limb weakness, or can be completely symptomless[3]. Some patients with HGPS suffer renal infarction[6] or amputation of toes because of spontaneous gangrene[7].

Some HGPS individuals have significant electrocardiographic (ECG) abnormalities or left ventricular hypertrophy. Sonographic and ECG evidence of myocardial ischemia is not common initially, but after a few years echocardiograms and carotid Doppler sonography may show calcification of the aortic and mitral valves and hypertrophy of the intimal layer of the internal carotid artery[8]. Systemic hypertension is common and may occur before the age of 5 years[4]. Ankle-brachial indices reflecting vascular compliance are abnormal in most cases[9-10], which indicates that the vascular function of HGPS individuals is diminished and that

accelerated vascular stiffness is an early and important mechanism of vascular disease.

1.2 Pathological Changes of the HGPS Cardiovascular System

1.2.1 Arterial Pathological Changes

Autopsy has shown widespread and severe premature atherosclerosis in HGPS patients, both of which appear to be critical factors contributing to death[11-12]. Advanced coronary atherosclerotic lesions and healed or recent MI have been reported. The arteries are usually stenosed or occluded by plaques or narrowing of intramural arteries[11]. Occlusion of the right coronary artery is especially common[4], as are lesions of the left anterior descending artery. In some patients, coronary dysfunction occurs acutely over weeks or even hours. There are also HGPS patients with very focal or absent plaque formation and obstruction[3]. Whether the coronary atherosclerosis is accompanied by smooth muscle cell (SMC) loss is controversial. Although an HGPS rodent model shows prominent SMC dropout from the media, this phenomenon is not prominent in human coronary artery[12]. Intimal fibrosis, marked adventitial fibrosis and medial thinning subjacent to thick plaque, with or without extensive calcification, have also been reported[12-13].

The aorta of HGPS individuals may also display severe atherosclerosis, which may result in increased stiffness and decreased compliance, with findings ranging from an almost normal appearance to severe atheromatosis[3]. Researchers have recently observed thickened intima, thickened adventitia and degenerated media with approximately 50% loss of medial SMCs in the ascending aorta[12]. Progressive atherosclerosis of intracranial vessels is believed to be responsible for the formation of epidural hematomas. The findings of Stehbens et al., following their histological and ultrastructural study of vascular tissue obtained from a progeric woman with traumatic subdural hemorrhage, support the view that the responsible changes are atherosclerotic[14]. These changes can lead to intracranial hematoma formation even after a mild head injury. Tortuous temporal arteries and thickened and tortuous peripheral arteries have also been reported. Other pathological findings in HGPS individuals include fibrous lesions, rich in collagen and proteoglycans[12]. Stehbens et al. detected collagen types III, IV, V, VI, and I in the aorta and renal vessels from two autopsies of progeria cases, which is consistent with the presence of atherosclerotic disease[14].

These facts strengthen the belief that HGPS and cardiovascular disease might share common features in their pathogenesis.

1.2.2 Valvular Changes and Pulmonary Hypertension

Cardiac murmurs in HGPS individuals probably result from arteriosclerosis involving predominantly the mitral valve, the aortic valve and the left ventricular outflow tract[4]. The valve leaflets may be thickened and calcified[3], and such calcification should be noted. Highly accelerated calcific deposition occurs in the mitral annulus and aortic valve cusps in addition to the coronary, aortic and cerebral arteries[12]. The calcification of valvular tissue, representing extensive degenerative changes, is an exaggeration of the valvular changes of normal aging.

Attention should also be paid to pulmonary arterial lesions in HGPS individuals. Significant medial hypertrophy of the pulmonary arteries with intimal fibrosis and thickening resulting in fatal pulmonary hypertension has been reported[15]. Histopathologic findings from the autopsy of HGPS individuals showed abnormal deposition of collagen and elastic fibers, as well as cellular proliferation, in the intima of pulmonary small arteries[15-16].

2. MOLECULAR BIOLOGICAL MECHANISM OF HGPS

HGPS was initially thought to be an autosomal recessive disorder. In 2003, however, Eriksson et al. found that the disease was not inherited and that mutations in the LMNA gene were responsible for the syndrome[17]. Most (approximately 80%-90%) cases of HGPS are caused by a de novo nucleotide substitution at position 1824 (C→T) in exon 11 of LMNA[17-18].

2.1 Lamin A

LMNA provides instructions for the production of lamin A and lamin C by alternative splicing; these constitute the major protein component of a 20 nm filamentous meshwork called the nuclear lamina located inside the inner nuclear membrane in most differentiated cells[19]. Lamin A is also located throughout the nucleoplasm and interacts not only directly with chromosomes but also with many structural and signaling proteins, including components of the nucleus and proteins linking the nucleoplasm to the cytoplasmic cytoskeleton. Lamin A seems to play fundamental roles in maintaining the integrity and shape of the nuclear envelope and

the nuclear pore complexes, global regulation of transcription, DNA replication, DNA repair, cell cycle control, cellular differentiation and chromatin organization[20-22].

Lamin A is synthesized from a 664 amino acid precursor protein called prelamin A, which is processed through a series of post-translational modifications to become mature lamin A. The steps include[17]: farnesylation of the cysteine in the C-terminal CaaX motif by farnesyl transferase; proteolytic cleavage of the aaX terminus by the zinc metalloprotease ZMPSTE24 (also named FACE1); methylation by isocarboxymethyl transferase; and second cleavage of the remaining 15 C-terminal prelamin A residues (647-661), which remain farnesylated and are methylated by ZMPSTE24. Mature lamin A is not farnesylated.

2.2 Mutations and Process of Progerin Production in HGPS

The classical mutation of HGPS LMNA (1824C>T, p.G608G) does not alter the encoded amino acid sequence; that is, the mutation is silent. This mutation partially causes a cryptic splice donor site (c. 1819-1820) in exon 11 of LMNA, leading to the production of a prelamin A mRNA that contains an internal deletion of 150 base pairs. This transcript is then translated into a mutant lamin A protein termed progerin that lacks 50 amino acids (607-656) near its carboxyl terminus end[17]. Because the second endoproteolytic cleavage site recognized by ZMPSTE24 lies in this missing region, the progerin cannot undergo complete maturation and retains its C-terminal farnesylation motif permanently[1,17]. Mature lamin A continues to be produced in HGPS individuals[1].

Other mutations causing typical HGPS have been reported; for example, 1868C>G (T623S) at exon 11 in LMNA produces lamin A with a 35 amino acid truncation that completely overlaps the 50 amino acid truncation[24-25]. 1822G>A (G608S) at exon 11 in LMNA leads to the same cryptic splice effect producing 50 amino acid truncated lamin A[17].

Mutations at exon 2, 8, or 9 of LMNA result in unusual cases of HGPS (e.g. absence of coronary artery disease[26]), as do mutations in ZMPSTE24[27]. Thus, the typical HGPS phenotype with cardiovascular disease seems to be caused by mutations in exon 11. Additionally, the length of the amino acid truncation may be related to the severity of HGPS: the 50 amino acid truncation of the G608G mutation may be more harmful than the 35 amino

acid truncation of the T623S mutation, which grants a longer life span[24].

2.3 General Mechanisms of the Molecular Biology of HGPS

2.3.1 Cellular Phenotypes and Abnormalities

Interestingly, cells from HGPS patients have a markedly reduced replicative life span compared with normal cells and develop typical nuclear morphologic changes when grown in culture. The structural integrity of the inner nuclear membrane seems to be disrupted and the envelope shows "blebbing" morphologically. Other cellular phenotypes include thickening of the nuclear lamina, loss of peripheral heterochromatin, mislocalization of the nuclear protein[18] and clustering of transport channels, or nuclear pores, in the nuclear membrane[28].

HGPS cells show an impaired ability to maintain their genome integrity, exhibiting defective DNA repair, accumulation of DNA damage and altered gene expression. Before developing obvious nuclear morphologic changes, HGPS fibroblasts exhibit broad abnormalities in histone modification patterns and global changes in gene expression. The expression level of 361 genes was shown to be upregulated for transcription factors, extracellular matrix proteins and proteins implicated in atherosclerosis and was downregulated for proteins involved in DNA replication and chromatin remodeling[29]. HGPS fibroblasts also show a delayed checkpoint response, defective DNA damage repair and increased sensitivity to various DNA-damaging agents such as radiation[30]. Multiple chromatin organization changes have also been described. HGPS cells exhibit loss of peripheral heterochromatin, with the upregulation of some constitutive heterochromatin and downregulation of some facultative heterochromatin[16]. The redistribution of heterochromatin may decrease DNA repair and increase genome instability. Previous studies have identified differentially expressed mRNAs that are mostly related to genes for DNA synthesis, DNA repair, the cell cycle, fatty acid oxidation, the extracellular matrix and chromosome processing[9,22]. Recent studies of cultured HGPS fibroblasts have also identified 30 differentially expressed proteins, categorized into five groups: cytoskeleton, regulation of apoptosis, methylation, calcium ion binding, and duplication, with increased concentrations of free cytosolic calcium[31]. Transport of proteins from the cytoplasm into the

nucleus was found to be reduced in cells with HGPS gene mutations[32].

Progerin expression also induces multiple mitotic abnormalities, including cytokinesis delay, abnormal chromosome segregation and binucleation[33-36]. The G1 phase of the cell cycle was elongated in HGPS cells[31]. The nuclear location of interphase chromosomes in HGPS fibroblasts differs from that in control proliferating cells and mimics that of control quiescent fibroblasts, with smaller chromosomes toward the nuclear interior and larger chromosomes toward the nuclear periphery[35].

In conclusion, HGPS has been shown to affect many fundamental cellular functions including heterochromatin organization, mitosis and DNA replication, transcription and repair. The genetic and protein processing defects in HGPS are well understood, but the mechanism of the cellular defects resulting from mutations in LMNA is undefined. One popular hypothesis is that the disruption of the structural and functional integrity of the nuclear lamina is critical for the pathological changes[18]. The defects in the nuclear lamina might be transduced into cellular changes by mislocalization of TPR to the cytoplasm, abnormal meshing of intermediate filament proteins lining the inner nuclear envelope[31], or abnormal interactions with other cellular proteins or abnormal chromatin structure[23].

2.3.2 What is the Principal Culprit?

It is widely thought that it is not the change in mature lamin A but the presence of progerin that is the underlying deleterious agent in HGPS. The progerin level of primary dermal fibroblasts from HGPS patients was 160 times higher than that in unaffected controls, whereas the level of lamin A was not affected[36]. Progerin has been shown to cause the aberrant nuclear morphology typical of HGPS cells in the presence of wild type lamin A, evidence suggesting that progerin acts in a dominant negative manner. The level of progerin expression in HGPS cells could be an important determinant of disease severity, as indicated by observations in patients, mouse models and cultured cells[37].

However, the exact roles of progerin in the etiology of the disease are controversial. The presence of the farnesyl group in the progerin molecule, and not a change in amino acid sequence, is thought to be the principal culprit in the pathogenesis of HGPS[38]. The accumulated prelamin A with retention of farnesylation persists in the nuclear periphery, tethered owing to an association of the hydrophobic prenyl group with the nuclear envelope, might increase the membrane's lipophilicity accordingly[28,31,39-40]. The cellular dysfunction can be ameliorated in several ways affecting the progerin molecule, including the application of a protein farnesyl transferase inhibitor that blocks the farnesyl attachment[41], an antisense morpholino-based therapy that prevents the abnormal splicing and decreases the progerin level[42], and rapamycin[43-44], which enhances progerin clearance. A mouse model expressing non-farnesylated, full-length prelamin A is reported to exhibit no progeria-like disease phenotypes (although the animals eventually developed cardiomyopathy and sudden death)[45]. Such evidence indicates that the presence of the farnesyl group is the underlying deleterious agent in HGPS. A differing opinion comes from several reports that suggest that mice expressing non-farnesylated progerin (LmnanHG/+ mice, in which progerin's carboxyl terminal CSIM motif is changed to SSIM), also develop severe progeria[38,46]. It is speculated that the ability of non-farnesylated progerin to elicit disease depends on the carboxyl terminal mutation used to abolish protein prenylation[46].

3. MOLECULAR MECHANISMS IN THE CARDIOVASCULAR SYSTEM

As mentioned above, atherosclerotic disease is the primary cause of death in HGPS, but how the gene mutation in LMNA causes the tissue-specific abnormalities associated with HGPS remains unclear.

The disposition of progerin may indicate a direct or indirect link between progerin expression and cardiovascular disease. Limited data from skin biopsies show that progerin is mainly located in vascular SMCs (VSMCs), endothelial cells (ECs), dermal fibroblasts and keratinocytes. Biopsies of HGPS patients' coronary arteries also demonstrate that progerin is well represented in all layers, including most medial VSMCs, intimal plaque, adventitial fibroblasts and ECs[12]. Zhang et al. reported that the highest levels of progerin were found in HGPS-derived mesenchymal stem cells (MSCs), VSMCs and fibroblasts, with slightly less in ECs and very little in neural progenitors[18]. Progerin disposition might thus indicate the tissue-specific abnormalities of HGPS individuals.

HGPS shows the hallmarks of a specific developmental disorder affecting mesodermal and mesenchymal cell lineages. In HGPS patients, VSMCs

and MSCs, which are widely thought to maintain vascular circulation, show defects in differentiation and increased sensitivity to mechanical stress and hypoxia *in vitro* and *in vivo*[18]. Because the arterial vasculature is exposed to an array of mechanical stresses, including shear stress, pressure and strain, the defects are important for atherosclerosis. Transgenic mice carrying the G608G mutation display dramatic and progressive loss of VSMCs in the media of large arteries[13]. In an autopsy study of HGPS patients, loss of VSMCs in the media of large arteries was also observed. A young patient with progeria typically has fewer MSCs and VSMCs than unaffected children[18]. Apoptosis, senescence of VSMCs and/or a shortage of MSCs needed for tissue replacement in the cardiovascular system might play an important role in the pathogenesis of the premature atherosclerosis.

The disordered connective tissue may partially contribute to the atherosclerotic disease of HGPS characterized by highly abnormal vessel wall extracellular matrix (ECM), including adventitial fibrosis[12]. Microarray studies of HGPS have indicated significant misregulation of transcripts encoding ECM proteins[18], and the altered ECM is likely to be a major downstream component driving the disease. It is also reported that the expression of several genes involved in building and maintaining the ECM are altered, including several collagens, proteoglycans and matrix metalloproteinases (MMPs)[29,47]. Of particular note, MMP-3 mRNA in HGPS fibroblasts is downregulated more than any other ECM gene when compared with donor age-matched controls[47]. The decrease in MMP-3 correlates with disease severity *in vivo* and the decreased MMP-3 level suggests an altered balance in connective tissue remodeling in HGPS[2].

4. RELEVANCE OF PROGERIA TO NORMAL AGING

The most fascinating aspect of research into the pathogenesis of HGPS is that HGPS may represent a form of premature aging and share a common mechanism with geriatric cardiovascular disease. Clinically, HGPS has several symptoms resembling normal aging, including growth retardation, alopecia, diminished subcutaneous fat and progressive atherosclerosis. The cell types and pathological changes involved are also similar: both typical atherosclerosis and HGPS exhibit global atherosclerosis, calcification, inflammation and evidence of plaque erosion or rupture[12].

Interestingly, several studies have demonstrated that progerin mRNA and protein are also present at lower levels in cells and tissues during the process of normal aging and increase with age, which suggests that the same HGPS cryptic donor splice site is active, though less so, and can lead to accumulation of progerin over time[48]. Progerin mRNA and protein have been shown to accumulate with increasing cell passages and donor age *in vitro*[33,36,48,49], and *in vivo* fibroblasts from an older person were found to contain more progerin than fibroblasts from a younger person[48]. It is reported that progerin-positive cells reside in non-HGPS arteries and that progerin increased by an average of 3.3% per year in coronary arteries, according to autopsies of non-HGPS individuals aged 1 month to 97 years[12]. Previously, it was found that progerin-expressing cells in normal skin were restricted to a subpopulation of dermal fibroblasts and terminally differentiated keratinocytes[12,49] that might characterize a possible terminal differentiation phenotype *in vivo*. Moreover, normal cells of physiological aging with progerin expression have cellular phenotypes that resemble aspects of HGPS cells *in vivo* or cells that have been passaged repeatedly *in vitro*[36]. These findings suggest that progerin expression and cellular senescence might be intimately linked and have certain cellular and molecular mechanisms in common.

Further evidence that progerin production might be involved in the process of physiological aging is an interesting inverse correlation between progerin transcription and immortalization of several cell lines[50]. The nuclear abnormality can be reversed by inhibition of the splice site. It has been demonstrated that changes in the splicing ratio of lamin A and progerin is the key factor in life span, because heterozygous mice harboring the mutation lived longer than homozygous littermates but for a shorter time than the wild type.

In conclusion, HGPS and normal geriatric individuals show much concordance in terms of symptoms, pathological changes and progerin expression and distribution. This concordance suggests that progerin plays a role in physiological aging in the general population. However, the cause-and-effect relationship between progerin and physiological aging remains unclear and the underlying mechanism is therefore of great interest.

The accumulation of progerin seen in the nuclear lamina of HGPS cells may contribute to pathophysiologic changes in normal cells. It has been

reported that cells from HGPS individuals exhibited altered histone modification[21] and increased DNA damage, which is similar to the process of normal aging[29,48]. Interestingly, progerin-positive normal fibroblasts exhibit mitotic defects seen in HGPS cells that increase with the number of passages[36,49], which indicates a possible correlation between progerin-induced mitotic defects and physiological aging.

The most encouraging evidence linking progerin and normal aging comes from studies on the close relationship between progerin and telomeres. Telomere defects are widely believed to be a causative factor in cellular senescence. In 1992, Allsopp et al. found that telomere lengths were relatively reduced in HGPS fibroblasts[51]. Huang et al. demonstrated that fibroblasts overexpressing mutant lamin A exhibited accelerated telomere shortening and reduced replicative life spans, in addition to abnormal nuclear morphology[52]. The telomeres of skin fibroblasts from HGPS individuals were also shown to be shorter than those of age-matched controls[53]. The latest research addresses various aspects of the possible biological connection between progerin production and telomere damage[50]: non-HGPS fibroblasts expressing progerin had shorter telomeres and exhibited greater senescence-associated β-gal activity; progerin production was not induced in immortalized cells or in telomere-independent, oncogene-driven premature cellular senescence; forced elongation of telomeres in normal fibroblasts resulted in significant downregulation of progerin production; and elevated levels of progerin were induced in fibroblasts with uncapped telomeres. The relationship between progerin and telomeres is bilateral, according to reports that progerin might induce an acute DNA damage response on telomere dysfunction before telomere attrition is detectable[54]. Taken together, these results strengthen the conclusion that there is an inverse correlation between telomerase expression and progerin production and suggest that telomeres act as an upstream signal to regulate progerin production[50].

Although there seem to be many commonalities in the clinical and pathogenic features of HGPS and aging, other reports show many differences. HGPS does not accelerate all aspects of normal aging; that is, other degenerative symptoms such as cataract, diabetes, cancer, neural degeneration and immune dysfunction are less frequently observed, and HGPS combines symptoms of delayed maturity and immaturity[9,39]. Classical risk factors such as hypercholesterolemia, increased serum high sensitivity C-reactive protein, early stage hypertension and smoking are also absent in HGPS[12]. Researchers have identified more prominent adventitial fibrosis in the large, medium and small arteries and the veins of HGSP individuals, which would lead to diminished vascular compliance, increased vessel stiffness and potential predisposition to formation of intimal plaque[12]. The HGPS expression profile shows many important differences from the profile of fibroblasts passaged into replicative senescence, including proliferation and inflammatory response[29]. Of particular note is the observation that significant changes in the expression of transcription factors in HGPS, especially those involved in the development and differentiation of mesenchymal cells, are absent in senescent fibroblasts. The amount of progerin is about 160-fold higher and the combined amount of lamin A and progerin is about twice as great in HGPS individuals as in age-matched controls[36]. The progerin level of physiologically aging cells and tissues is much lower than that in HGPS individuals.

Thus, whether HGPS really is an accelerated aging syndrome or merely exhibits certain aspects of aging through different mechanisms continues to be debated. Most researchers believe that HGPS and normal aging at least share similar pathophysiologic processes, and therefore HGPS might provide opportunities to explore the mechanisms of normal aging and age-dependent disease.

In conclusion, elucidating the pathogenesis of and finding effective treatments for HGPS has fascinated clinicians and researchers for several decades, not just because of the distress that the syndrome causes affected children and families, but also because it provides insights into the process of normal aging and age-related cardiovascular disease. Progerin could be considered a marker of aging, and therapeutic strategies for HGPS may be useful in preventing normal aging and age-related cardiovascular disease. HGPS may serve as a model of aging accelerated to occur over a few years compared with the several decades required for normal aging. Hence, researchers have a rare opportunity to elucidate the mechanism of aging and find ways to slow the process, for the benefit of HGPS patients and for all people.

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