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Progeria of Stem Cells: Stem Cell Exhaustion in Hutchinson-Gilford Progeria Syndrome

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Hutchinson-Gilford progeria syndrome (HGPS) is a rare, fatal genetic disorder that is characterized by segmental accelerated aging. The major causal mutation associated with HGPS triggers abnormal messenger RNA splicing of the lamin A gene leading to changes in the nuclear architecture. To date, two models have been proposed to explain how mutations in the lamin A gene could lead to HGPS, structural fragility and altered gene expression. We favor a compatible model that links HGPS to stem cell-driven tissue regeneration. In this model, nuclear fragility of lamin A-deficient cells increases apoptotic cell death to levels that exhaust tissues' ability for stem cell-driven regeneration. Tissue-specific differences in cell death or regenerative potential, or both, result in the tissue-specific segmental aging pattern seen in HGPS. We propose that the pattern of aging-related conditions present or absent in HGPS can provide insight into the genetic and environmental factors that contribute to normal aging.

HUTCHINSON-GILFORD progeria syndrome (HGPS) is a rare genetic disease characterized by very early onset of features associated with normal aging (1). In affected individuals, aging-related phenotypes seem to proceed at an approximately 7-fold accelerated pace, leaving young children with the appearance and health conditions of their grandparents. HGPS affects about 1 in 8 million children, with just over 100 cases reported in different populations around the world.

HGPS patients usually appear normal in early infancy. It is between 9 and 24 months of age that affected infants begin to experience profound growth delays that result in short stature and low body weight. Characteristic features of HGPS include a distinctive facial appearance due to mandibuloacral dysplasia (MAD), loss of hair and subcutaneous adipose tissue, hip dislocations, skeletal defects, and other abnormalities (1–3). Pathologically, children with HGPS suffer from generalized atherosclerosis and cardiovascular disease and die of myocardial infarction or stroke at an average age of 13 years (4,5).

The clinical features seen in HGPS strikingly resemble certain aspects of natural aging (2). HGPS patients do not display all attributes associated with old age, however. HGPS and other diseases in which only some aspects of normal aging appear accelerated are referred to as segmental progeroid syndromes (6). Metabolic, endocrine, and immunologic examinations of HGPS patients reveal no uniform abnormalities. No signs of precocious brain aging are observed; individuals have normal intelligence and emotional development. There is no measurable cognitive degeneration or neurosensory decline, and no formation of cataracts, diabetes, or hyperlipidemia. Most strikingly, malignancies are not associated with HGPS.

Lamin Proteins and the Nuclear Envelope

Nuclear lamins are grouped as A-type or B-type lamins on the basis of their biochemical properties and behavior during mitosis (7). These proteins, which constitute a class of intermediate filaments, are components of the nuclear lamina, the innermost layer of the nuclear envelope. The nuclear lamina is a protein network that maintains the structural integrity of the nuclear envelope and interacts with chromatin (8). B-type lamins are expressed in all cells during development and are essential for cell viability. Four A-type lamin proteins arise from a single gene (LMNA) by alternative messenger RNA splicing, with lamin A and lamin C being the major protein products. Lamin A is encoded by exons 1–12 of the LMNA gene; the immature lamin A protein is farnesylated near the C terminus, which is subsequently cleaved off by a specific proteinase, ZMPSTE24, to form the mature protein. Lamin C is derived by use of an alternative splice site in intron 10 to produce a shorter protein (9). Lamins A and C form either homodimers or heterodimers to create the filamentous structure of the nuclear lamina (7,10).

HGPS and LMNA

Mutations in LMNA are associated with numerous human sporadic or hereditary diseases, including Emery-Dreifuss muscular dystrophy types 2 and 3, limb-girdle muscular dystrophy, Charcot-Marie-Tooth disease type 2B1, Dunnigan-type familial partial lipodystrophy (FPLD) type 2, and others (11) for which genotype and/or phenotype relationships have been deduced (12). HGPS results from specific de novo mutations in LMNA [reviewed in (3)] (13,14). A recurrent, dominant, de novo G608G mutation found in approximately 90% of HGPS patients activates a cryptic splice site in intron 11 that results in an aberrant transcript that encodes a mutant LMNA protein with a 50-amino-acid internal deletion. This mutant protein retains a farnesylation site but lacks the proteolytic cleavage site. In heterozygous HGPS patients, this improperly processed

protein is thought to interact aberrantly with lamin C and with normal lamin A molecules from the wild-type allele to lead to nuclear instability.

Studies by Scaffidi and Misteli (15) generalize the contribution of aberrant nuclear architecture to normal aging. They showed that the HGPS-causing cryptic splice site is sporadically used in cells from healthy individuals, and demonstrated age-dependent aberrations in nuclear morphology. They propose shared mechanisms involving lamin A and nuclear architecture between HGPS and physiological aging (15) [reviewed in (16)]. Recently, advances have been made in treatment options for HGPS, including the use of farnesyl transferase inhibitors (17) and modified antisense oligonucleotides to block the cryptic LMNA splice site (18).

HGPS fibroblasts show strikingly altered nuclear shapes and sizes, sometimes accompanied by chromatin extrusion (14). Nuclei defective in lamins are mechanically fragile and susceptible to nuclear damage and cell death (19,20). Lamin A/C-deficient mouse embryo fibroblasts that are subjected to mechanical strain show increased nuclear deformation, defective mechanotransduction, and impaired viability (21). This fragility could explain the cardiac-muscle and skeletal-muscle pathologies of HGPS patients, as resulting from mechanical damage during muscle contraction.

The nuclear envelope is also involved in regulating gene expression patterns by organizing heterochromatin within the nucleus (22). Lamin A/C proteins are thought to regulate the activity of tissue-specific transcription factors, and it is also speculated that these proteins bind core histones and therefore influence tissue-specific expression patterns (11). Furthermore, lamins A and C have been found to bind directly to several transcriptional regulators, including retinoblastoma protein (pRB) (23). Uncoordinated change of gene expression programs by mutant lamin A is likely to have deleterious effects (11). For Lmna mutations leading to muscular dystrophy in mice, it was proposed that both structural weakness of cells and impaired satellite cell differentiation due to altered gene expression contribute to disease progression (24). In HGPS, mechanical weakness of cells, altered gene expression, or other mechanisms could contribute to cell attrition and stem cell exhaustion.

Insights From Mouse Models

Transgenic mice carrying a human LMNA gene containing the common HGPS mutation show progressive loss of vascular smooth muscle cells in large arteries and early death from atherosclerosis (25). As noted by Varga and colleagues, the observation of atherosclerosis as the major disease feature of these mice may reflect the exceptionally high mechanical stress on the cardiovascular system, which may cause this tissue to be the most susceptible to lamin A deficiency; this observation is consistent with atherosclerosis being the most common cause of death of HGPS patients. Mice homozygous for an autosomal recessive mutation of the *Lmna* gene ($Lmna^{L530P/L530P}$) that replaces the normal mouse gene with one that causes a complex splicing abnormality show symptoms resembling those of HGPS patients as well as premature death of terminally differentiated mesenchymal cells (26). Different aspects of the varied phenotypes of several mouse models reflect either the absence of both lamin A and lamin C, which in $Lmna^{-/-}$ mice produces symptoms similar to Emery-Dreifuss muscular dystrophy (22) or presence of an allele that produces progerin (27), suggesting that lamin A mutations leading to progeria are dominant, gain-of-function alleles (28). Recently, Fong and colleagues (29) showed that mice that lack lamin A but produce lamin C appear normal [reviewed in (30)], implying that lack of lamin C proteins may be more critical than previously suspected.

Other insights regarding lamin A come from studies of mice lacking the proteinase that cleaves the farnesylated protein. Knockout of the Zmpste24 gene produces a phenocopy of most defects seen in $Lmna^{HG/+}$ mice, along with disease phenotypes consistent with HGPS and human laminopathies (31–33).

LMNA Expression and Stem Cells

Although B-type lamins are ubiquitously expressed in all cell types, the expression of A-type lamins is developmentally regulated. Generally, A-type lamins are absent from the early embryo, early embryonic stem cells, and stem cells of the hematopoietic and neuroendocrine systems (34,35). Hence, embryonic development of $Lmna^{-/-}$ mice is not affected by the absence of lamin A. Neonatal $Lmna^{-/-}$ mice are indistinguishable from their wild-type and heterozygous siblings (22), just as HGPS children appear normal as infants. Cells of postnatal and adult tissues of $Lmna^{-/-}$ mice are degenerate, however, and the animals die prematurely, just as HGPS premature aging begins as a growth delay before the age of 2 years and results in premature death.

HGPS and Stem Cell Exhaustion: A Model for Segmental Aging

Because HGPS patients experience only about one-seventh the average normal life span, we hypothesize that cell turnover and cell death are also accelerated about 7-fold. This notion is supported by in vitro studies of HGPS fibroblasts in which a 4-fold to 8-fold increase in apoptosis was reported (36). Nuclei of cells harboring LMNA mutations are fragile, unstable, and highly susceptible to mechanical stress. Accumulation of structural changes and chromatin deterioration likely increases the level of DNA damage (37) and can lead to apoptosis. Although substantial work was done to characterize progeria mouse models, it is still tenuous whether the observed tissue damage and premature cell loss is due to programmed cell death.

Several authors including Prolla (38) and Warner (39–41) have previously proposed the involvement of progenitor cells or inadequate cell replacement in HGPS. Warner (41) has argued that lamin A mutations disrupt the nuclear envelope and drive cells into apoptosis. In an insightful review of models of accelerated aging, Warner and Sierra (39) discussed possible associations between increased cell loss and failure of cell replacement in xeroderma pigmentosum complementation group D (XPD)-deficient or $p53^{+/m}$ mice. Mutant mice with defects in XPD, p53, or Ku-80

Table 1. Common Age-Related Diseases PRESENT in Hutchinson-Gilford Progeria Syndrome (HGPS)

Disease	Mechanism	Stem Cell Relevance	Proposed Reason for Presence of Disease in HGPS	References
Atherosclerosis	Deposits of cellular waste products and calcium in the inner artery lining	Endothelial progenitor cells (EPCs) contribute to vascular regeneration and repair to replace damaged heart muscle cells and establish new blood vessels	Premature exhaustion of endothelial progenitor cells; mechanical stress on cells increases apoptosis and tissue regeneration	47,48
Cardiovascular Disease	Dysfunctional conditions of the heart, arteries and veins			49,50
Lipodystrophy	Selective loss and redistribution of body fat, loss of subcutaneous adipose tissue	Human adipose tissue is a rich source of Multipotent Adipose-Derived Stem (hMADS) cells	Decline of tissue regeneration through depletion of adipose-derived stem cells	51
Alopecia	Hair follicles become dormant and the remaining hairs become thinner and sparser	Follicular hair stem cells can give rise to both the hair follicle and the epidermis	Baldness occurs when hair growth, which is dependent on hair follicle stem cells, fails to keep up with hair loss	52
Defects of nails	Damage to finger nail stem cells and their transient amplifying cell progeny	Stem cell pool supplies cells for rapidly growing finger nails	High cell turnover depletes rapidly dividing finger nail stem cells	53
Joint stiffness	Deterioration of ligaments and tendons constricts the joint's frictionless movement	Cartilage (chondrocytes) progenitor cells are responsible for joint regeneration	Decline of tissue regeneration through depletion of cartilage progenitor cells	54
Delayed dentition, malformation of teeth	Potential developmental defects in dental stem cell migration or activation			55

function show high rates of apoptosis and die prematurely (42–44). These mice share features with well-characterized premature human aging syndromes, especially Werner and Bloom syndromes, dyskeratosis congenita, and xeroderma pigmentosum (45).

In a review of gene expression analyses in progerias, Prolla (38) suggested that the regenerative capacity of tissues with high cell turnover might be reduced due to exhaustion of progenitor cells. We further expand upon this idea by proposing that this hypothesis explains not only the premature aging phenotype of HGPS but also the specific segmental nature of this progeria.

Why do HGPS patients show loss of hair and subcutaneous adipose tissue, hip dislocations, and skeletal defects, but not brain aging (Alzheimer's disease, cognitive degeneration, neurosensory decline), cataracts, type 2 diabetes, hyperlipidemia, or cancer (1,46)? Some of the age-associated conditions that are, or are not, seen in HGPS are listed in Tables 1 (47–55) and 2 (56–62), respectively. We propose that tissues for which stem cells are prerequisites for regeneration and repair of ongoing damage, those which undergo continuous mechanical stress (such as blood vessels and joints), or those which are required to support continuous growth (hair follicles, nails) correspond to those tissues that degenerate in HGPS patients. In contrast, diseases associated with tissues that are shielded from mechanical stress (brain), or for which the main assault requires decades of exposure (cataract formation, type 2 diabetes, hyperlipidemia) are absent from HGPS. Interestingly, premature decline of skeletal muscle is not seen in HGPS. The observation that this cell type, which clearly undergoes mechanical stress, is unaffected may reflect the less frequent stress on a voluntary muscle than on the more consistently stressed smooth muscle of the cardiovascular system, particularly over the short life span of an HGPS patient.

The lack of cancer in HGPS is particularly informative, with the fragility of nuclei of HGPS cells causing increased apoptosis. This high apoptotic cell loss may deplete stem cell pools and forestall malignant transformation. This argument is also supported by cancer incidence rates in normal aging, which increase significantly between the ages of 40 and 80 years but plateau or even drop beyond that (56,57). The role of stem cells in tumor initiation and progression is now widely discussed, and first evidence has been published for breast and brain cancer (63,64). We suggest that beyond 80 years, adult stem cell pools are largely exhausted, causing a drop in cancer risk. Though the existence of neuronal stem and/or progenitor cells has been recently reported (58,59), the developed brain maintains high levels of tissue homeostasis, and cell divisions are rare. We suggest that brain tissue is exposed to minimal mechanical stress and is well protected from premature aging in HGPS patients.

Cataracts, type 2 diabetes, and hyperlipidemia are caused by mechanisms not related to tissue regeneration, consistent with their absence from HGPS. Lipodystrophy, or adipocyte degeneration, in contrast, is associated with lamin A mutations in FPLD and MAD (65–67). Insulin resistance and type 2 diabetes are associated with FPLD and MAD, but it is not clear whether this phenotype is a primary effect of the LMNA genetic defect or a secondary effect of the rapid degeneration of adipose tissue in these patients. Whereas clustering proteins cloud the eye lens in cataracts, diabetes and lipid disorders are mainly triggered by unhealthy lifestyle choices. We argue that these diseases occur independently of stem cell–associated regeneration and so are not observed in HGPS patients.

Table 2. Common Age-Related Diseases ABSENT in Hutchinson-Gilford Progeria Syndrome (HGPS)

Disease	Mechanism	Stem Cell Relevance	Proposed Reason for Absence of Disease in HGPS	References
Cancer	Uncontrolled and invasive cell growth	Tumor stem cells theory: cancers arise from stem cells (breast and neuronal stem cells)	Early exhaustion of stem cell pools protects from malignant cancer stem cells	56,57
Brain Aging (Dementia, Alzheimer's, Cognitive and memory impairment)	Amyloid plaque accumulation, neuronal cell loss, impaired neurotransmitter signaling	Neuronal precursor and stem cells	Low number of adult cell divisions and cell turn over, low mechanical stress. Sufficient number of neuronal stem cells to maintain tissue homeostasis	58,59
Cataracts	Clouding of the eye lens by protein clumping	Cataract formation is independent from stem cell regeneration; environmental risk factors include smoking, diabetes, UV radiation	Biochemical process that increases with age but is independent from regeneration on a cellular level	60
Diabetes mellitus type 2	Non-insulin-dependent diabetes, insulin resistance	Insulin resistance is independent from stem cell regeneration	Diabetes mellitus type 2 is often associated with unhealthy lifestyle, obesity and hypertension	61
Hyperlipidemia	Elevation of lipids (cholesterol, cholesterol esters, phospholipids, and triglycerides)	Hyperlipidemia is independent from stem cell regeneration	Hyperlipidemia is caused by lifestyle habits (obesity, smoking) or treatable medical conditions (diabetes, kidney disease)	62

Which HGPS Pathologies Can Be Explained by Lack of Tissue Regeneration?

Conditions that show clear correlations with stem cell-driven tissue regeneration, and are manifested in affected children, include atherosclerosis, cardiovascular disease, lipodystrophy, alopecia (hair loss), defects of nails, joint stiffness, and malformation of teeth (Table 1). Of these conditions, atherosclerosis and cardiovascular disease are the main causes of death in HGPS patients (68,69). The cardiovascular system is under continuous high mechanical stress, potentially leading to increased death of fragile lamin A-deficient cells. Traditional views of vascular regeneration have been challenged by the recent identification of endothelial progenitor cells (EPCs) that contribute to endothelial and smooth muscle maintenance and repair. Cardiovascular disease patients and HGPS patients show a continuing loss of EPCs, causing a decrease of endothelial repair capacity and vascular regeneration (47,48). Atherosclerosis in general, however, is mainly caused by lipid deposition attributable to lifestyle. Accelerated loss of mechanically challenged, lamin A–deficient cardiovascular cells would exhaust EPC pools. Ailments such as hair loss and lipodystrophy can be explained by high cell turnover and impaired replacement due to a depleted stem cell pool.

Currently, detailed knowledge about stem cell biology is largely unavailable for many adult stem cell niches. Further insight into mechanisms of stem cell-driven tissue regeneration is required to confirm premature stem cell exhaustion in specific tissues in HGPS.

Conclusion

HGPS is distinct from other progeroid syndromes in that lamin A is not a direct component of DNA repair protein complexes. Bloom, Werner, and Rothmund-Thomson syndrome patients are deficient in DNA helicases, and Fanconi anemia and xeroderma pigmentosum patients are deficient in other aspects of DNA repair (2). Instead of contributing to genomic instability that leads to increased cancer risk in these other syndromes, the lamin A mutations that underlie HGPS likely cause premature stem cell exhaustion that depletes specific tissues (while sparing others) to produce a highly segmental tissue-specific pattern of premature aging that is not associated with increased cancer risk. By contrast, systemic failure of DNA repair or DNA maintenance mechanisms is expressed throughout the body and generates a more global acceleration of aging.

In HGPS, it is the intrinsic aspects of aging that are accelerated, whereas those that are caused primarily by extrinsic exposures remain unaffected. If this hypothesis is shown to be correct, it will be valuable in identifying the aspects of aging that are avoidable through lifestyle modifications.

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