Hutchinson-Gilford Progeria Syndrome: Pathophysiology and Possible Treatments

Pearl Hersh

Abstract

Named after the two scientist who independently described the condition, Hutchinson-Gilford Progeria Syndrome (HGPS) occurs due to a mutation in the LMNA gene that codes for Lamin A, a filament protein that acts to form the nuclear lamina in the cell nucleus. This mutation is a single C-to-T substitution at nucleotide 1824 of the LMNA gene. As a result of this mutation, an abnormal protein named 'progerin' is synthesized instead of Lamin A, causing the nuclear membrane to be malformed. Since protein farnesylation is needed to target progerin to the nuclear rim, farnesyltransferase inhibitor has been proposed as a form of treatment that could reduce the occurrence of misshapen nuclei and alleviate HGPS symptoms.

Introduction

Aging is a process that's inevitable. Over a typical lifespan, the body loses its ability to maintain homeostasis and fight off disease. The elderly also experience atherosclerosis that can lead to strokes and myocardial infarctions. Arthritic joint pain and stiffness are also common, as is thinning of the skin. Researches have speculated about the precise physical changes in the body that manifest themselves as the process of aging (Burtner and Kennedy 2010).

The answer may lie in a very rare segment of the population who suffer from progeriod syndromes that cause accelerated aging. The most severe of this group is Progeria, which causes rapid aging in children and death by adolescence. The calculated mean lifespan in Progeria patients is only 13 years of age (Kudlow et al. 2007).

HGPS Pathophysiology

Hutchinson-Gilford Progeria Syndrome (HGPS) is caused by a de novo heterozygous point mutation, changing a GGC sequence to GGT in exon 11 of the LMNA gene. This mutation causes a 50 amino acid sequence deletion at the carboxyl terminus of prelamin A, producing a truncated progerin in the place of Lamin A (Neelam et al. 2012). Lamins are intermediate filament proteins that polymerize to form nuclear lamina, a meshwork forming the inner nuclear membrane. Lamin A belongs to the A-type lamins that includes Lamin A and Lamin C. Lamin C differs very slightly from Lamin A by its C-terminal extension, which has 90 less residues than Lamin A. Both Lamin A and C contribute to the shaping of the nuclear membrane. When progerin is present in place of Lamin A, the nuclear membrane takes on an abnormal morphology (Rakha, et al. 2011).

The Proteins of the nuclear lamina were once thought to play merely a structural role. Through studying diseases that affect these proteins, it has become apparent that they also play an important role in various cellular functions such as signal transduction and gene expression (Scaffidi and Misteli, 2006). Therefore, mutations affecting these proteins can have devastating effects on multiple organ systems in the body, as in the case of Hutchinson-Gilford Progeria Syndrome (HGPS).

HGPS is part of a group of rare diseases known as laminopathies, in which the proteins of the nuclear lamina are affected. These diseases all result from LMNA gene mutations and include lipodystrophy, muscular dystrophy, peripheral neuropathy and Progeria (Liu, et al. 2010). In lipodystrophy, symptoms begin at the onset of puberty and patients experience loss of subcutaneous fat, high cholesterol and type-II diabetes. Muscular dystrophy is similar in that symptoms appear close to puberty and cause progressive muscle wasting. Peripheral Neuropathy is a laminopathy that causes nerve dysfunction. Progeria is perhaps the most devastating of them all since symptom onset begins at a few months of age and death from cardiovascular

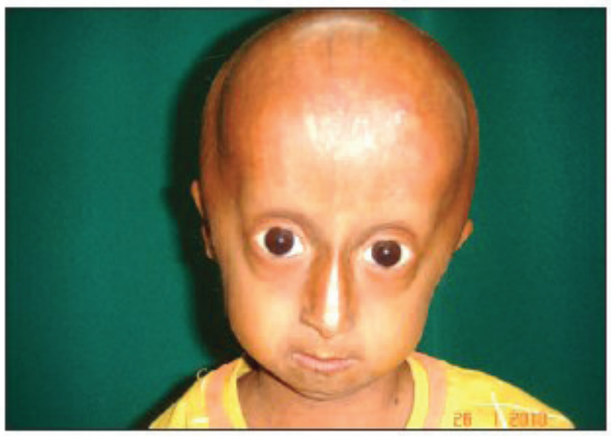
Perl Hersh graduated with a B.S. in Biology and will be attending New York Medical College .

illness is likely by age 13.

HGPS Phenotypes

HGPS disease symptoms include; slow growth, scleroderma-tous changes of the skin, alopecia, osteoporosis and atherosclerotic vascular disease. (Yang, et al. 2006) These symptoms contribute to a very distinctive look common to all Progeria patients. They are sometimes described as appearing like 'little aliens' due to their diminutive stature, lack of hair, and small heads with prominent noses.

Figure 1: Face of a Progeria patient showing alopecia, loss of eyebrow and eyelashes and prominent eyes with a tapered nasal tip. (Agarwal, et al. 2010)



In one particular Chinese girl with Progeria, HGPS diagnosis was made at 2 months of age. The child was the second-born of healthy parents with no remarkable family medical history. The first symptom that raised concern was a loss of subcutaneous fat in her abdomen and buttocks, where a baby would normally exhibit plumpness. Her hair was also unusually sparse and her veins were noticeably prominent for 2 months of age (Chen, et al. 2012).

At 2 years of age, the child had already lost all of her hair and was beginning to develop a characteristic Progeria face. Her forehead jutted out, her eyes were prominent and her jaw was undersized. Imaging studies taken over ages 4 and 5, showed patterns of bone resorption in her clavicles and distal phalanges along with hip displacement and dental crowding (Ibid).

The symptoms progressed rapidly and by age 6 the deformities caused speech and swallowing difficulties and hearing loss. When measured at age 8, she fell below the 3rd percentile in both height and weight compared to other her age and she remained very thin and small in stature (Ibid).

Diagnoses came later for an Indian boy who showed up at a Dermatology clinic at age 4. He had loss of hair, including eyelashes and eyebrows since age 1, and stunted growth. Doctors noticed his distinct prominent veins and eyes, beaked nose and high-pitched voice. His problems were far from merely dermatological, and he was diagnosed with Progeria after confirmatory imaging studies (Agarwal, et al. 2010)

Vertebrate Progeriod Models

Researchers attempting to better understand and treat Progeria, need models to work with. The incidence of Progeria is so infrequent in the population due to the rarity of the specific LMNA mutation that causes it. Nearly all Progeria patients in the world today are well known and have participated in studies by contributing medical data and samples. In the century or so since the discovery of the syndrome, only about 100 cases have been documented (Mohamed and Jayachandran 2009) and today, with only 48 known patients whose lifespans are short, these samples are severely limited.

Human Progeria research subjects are not only limited in number, it often isn't safe for them to participate in early stages of drug trials. Before a drugs potency can be determined, use in humans is unethical. Thus, creating animal models to test Progeria drugs is an important key to ultimately finding a cure.

After much trial and error, mice have been successfully genetically modified to be ZMPSTE24 deficient, causing the expression of Progeria-like symptoms (Osorio, et al. 2009). ZMPSTE24 is an enzyme that completes the post-translational processing of Pre-lamin A by cleaving it into its mature form of lamin A (Liu, et al. 2010). Without the ZMPSTE24 enzyme, Pre-lamin A processing is halted and this results in a truncated Lamin A protein similar to the progerin protein found in patients with HGPS.

Zebrafish models expressing truncated Lamin A

proteins have also been genetically engineered and studied. Using a splice-block method to delete the 8 amino-acid site of pre-lamin A cleavage in zebrafish embryos, researchers created progeriod zebrafish models. These zebrafish then exhibited accelerated aging and shortened lifespans along with other symptoms such as cell-cycle arrest and cartilage defects that appeared as craniofacial abnormalities (Koshimizu, et al. 2011).

Both the ZMPSTE24 deficient mice and the progeriod zebrafish models were genetically altered in a way where Lamin A was not able to be processed into its mature form. Another mouse model however, was modified so that it would not produce the Lamin A protein at all. This lamin A deficient mouse would only produce Lamin C, a similar Lamin protein normally produced alongside Lamin A. The Lamin C-only mice had no tissue abnormalities and appeared non-diseased (Fong et. al 2006).

In a state of complete lack of Lamin A, Lamin C seems to compensate and therefore, no pathologies result. It seems that the truncated, pre-lamin or progerin form of the Lamin A that accumulates when the protein's processing is halted, is the cause of the diseased cell (Fong et. al 2006). This realization can help researchers treat laminopathic diseases by developing drugs that can prevent immature lamin proteins from doing harm and possibly trigger the non-affected Lamin types (unaffected Lamin C in Progeria patients) to compensate for the missing protein.

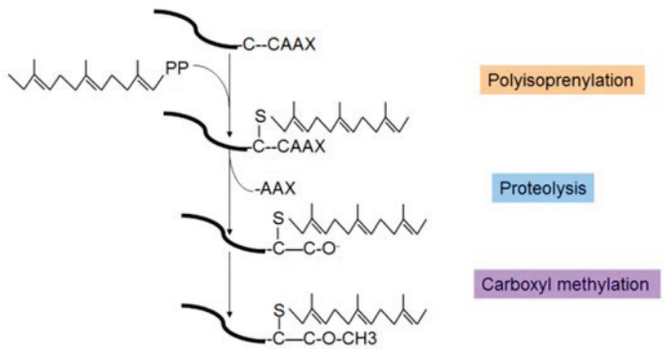
FTI Treatment

The advantage of farnesyltransferase inhibitor (FTI) is that it can mask HGPS symptoms even while the abnormal Progerin protein is still being expressed. By preventing progerin from attaching to the nuclear rim, FTI can increase the amount of normal-shaped nuclei (Capell, et al. 2005).

Prelamin A requires a 3-step prenylation processing to be converted into mature Lamin A. The prenylation occurs rapidly and unprocessed Prelamin A is barely detectable (Gao, et al. 2009). A similar form of post-translational modification occurs in all CaaX proteins. This category of proteins contains a specific amino acid sequence at the c-terminal consisting of a cysteine residue, 2 alipathic residues and another c-terminal acid 'x' that varies, hence the acronym 'CaaX Protein'. In Prelamin A, the CaaX terminal is made of cysteine, alipathic serine and isoleucine, and methionine (CSIM) (Dominici, et al. 2009).

In the first processing step of polyisoprenylation, farynesyltransferase recognizes methionine and adds a 15 carbon farnesyl to the CSIM sequence. Proteolysis is next, in which endoprotease ZMPSTE24 removes the 'SIM' portion of the CSIM sequence (Dominici, et al. 2009). In the final prenylation step, carboxyl methylation of the farnesylated prelamin A occurs via methyltransferase to produce carboxymethylated-farnesylated prelamin A (preLA-farnesyl-C-H_3).

Figure 2: Prenylation process of the CAAX proteins. The protein prenylation process includes 3 steps: polyisoprenylation, proteolysis, and carboxyl methylation. Polyisoprenylation is the attachment of an isoprenoid lipid by protein farnesyltransferase (FTase) or geranylgeranytransferase type I (GGTase-I) to CAAX box. In the second step, the CAAX residues are proteolysed by prenyl protein peptidase RCE1 family to release -AAX. This is followed by subsequent endoproteolytic trimming and carboxyl methylation significantly increases the hydropho-



Progerin, a truncated form of pre-lamin A, is missing the ZMPSTE24 cleavage site and will therefore retain the cysteine C-terminal that is farnesylated and carboxymethylated (Liu, et al. 2010). The retention of the toxic farnesyl group will cause progerin to incorporate itself into the nuclear envelope in an abnormal fashion. Once in the nuclear envelope, progerin will produce an abnormal heterochromatin assembly and lead to an increase in DNA

damage (Zaremba-Czogalla et al. 2011). Structurally, the nuclear membrane will also become misshapen and stiff. This characteristic is known as nuclear blebbing and is a distinct phenotype of progeria.

Lonafarnib, a farnesyltransferase inhibitor drug initially used for cancer treatment, has recently been tested on patients with HGPS in a clinical trial. In 2007, 25 progeria patients from 16 countries around the world came to Boston, Massachusetts over a period of 2 years to receive Lonafarnib. They were measured for changes in weight, skeletal rigidity, hearing and cardiovascular health. The study showed that the children improved in at least one or more of the measured areas over the course of the trial. Most importantly, in the essential area of cardiovascular health, which is the cause of death in progeria patients, all but one participant showed improvement (Gordon, et al. 2012)

Other Treatments

In the presence of farnesyltranferase inhibitors, the cell will often adapt and turn to other processing pathways such as grenygrenylation (Gordon et al. 2008). In place of polyisoprenylation (addition of a 15-carbon farnesyl) via farnesyltransferase, a similar enzyme, geranylgeranyltransferase I (GGTase I) can add a 20-carbon geranylgeranyl group to the Pre-lamin A (Sousa et al. 2008). This adaptation mechanism can lessen the effectiveness of FTI treatment. A combination of statins and aminobisphosphonates, combined with FTI treatment can inhibit both farnesylation and grenygrenylation pathways.

Although not originally developed for progeria, the statin Pravastatin and the aminobisphosphonate Zoledronic acid have been implemented in a 2012 clinical trial, along with FTI Lanofarnib, in progeria patients. Pravastatin, an HMG-CoA inhibitor, is often prescribed to lower cholesterol levels and keep atherosclerosis from worsening. Zoledronic acid is used in bone cancers and multiple myeloma, can help prevent hyepercalcaemia that occurs in Progeria patients. These two drugs work principally by preventing farnesyl group formation, a process vital to progerin in the course of the disease (Neelam et al. 2012).

Lastly, stem Cell use has been researched as a form of treatment. Since Lamin A expression is developmentally regulated, it isn't present in embryonic cells and stem cells (Mounkes et al. 2003). This can be seen in the normal appearance of Progeria-modeling mouse embryos and progeria patients up until a few months of age, when progerin starts to proliferate in cells in place of Lamin A. Stem cell use has been explored as a means of initiating tissue regeneration and offsetting the accelerated rate of cell aptosis that causes rapid aging in Progeria patients (Halaschek-Wiener and Brooks-Wilson 2007).

Conclusion

Progeria is a rare, devastating and terminal disease caused by a single gene mutation. Since the mutation is located on the LMNA gene, the Nuclear Lamina Proteins are affected. A single nucleotide substitution causes a 50 base pair deletion of pre-lamin A (Lain A pre-cursor). Lamin A is then prevented from completing its processing and remains in an immature form called progerin. The accumulation of progerin has a multi-systemic effect leading to rapid aging and early death from complications of atherosclerosis. Lonafarnib, a FTI inhibitor, has been proposed as a form of treatment and recent studies have shown it is effective in alleviating some of the symptoms of Progeria.

References

Agarwal U, Sitaraman S, Mehta S, Panse G. Hutchinson-gilford progeria syndrome. Indian Journal of Dermatology, Venereology and Leprology. 2010;76(5):591.

Burtner CR, Kennedy BK. Progeria syndromes and ageing: What is the connection? Nature Reviews.Molecular Cell Biology. 2010;11(8):567-78.

Capell B, Erdos M, Collins F, et al. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. Proceedings Of The National Academy Of Sciences Of The USA. September 6, 2005;102(36):12879-12884.

Chen C, Lin S, Lin D, Liu Y, Hsu LJ, Wang W. Clinical Imaging Findings In A Girl With Hutchinson-Gilford Progeria Syndrome. Genetic Counseling. 2012;23(1):1-7.

Dominici S, Fiori V, Magnani M, et al. Different prelamin A forms accumulate in human fibroblasts: A study in experimental models and progeria. European Journal of Histochemistry : EJH. 2009;53(1):43-52.

Fong LG, Ng JK, Lammerding J, Vickers TA, et al. Prelamin A and lamin A appear to be dispensable in the nuclear lamina. J Clin Invest. 2006;116 (3):743-52.

Gao, Juehua, Liao, Jie, Yang, Guang-Yu. CAAX-box protein, prenylation

process and carcinogenesis. American Journal of Translational Research. [serial online]. 2009. 1(3): 312–325.

Gordon, Leslie B., Kleinman, Monica E. et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome. Proceedings of the National Academy of Sciences.2012;109(41).

Gordon LB, Harling-Berg C, Rothman FG. Highlights of the 2007 progeria research foundation scientific workshop: Progress in translational science. The Journal of Gerontology. 2008;63A(8):777-87.

Halaschek-Wiener J, Brooks-Wilson A. Progeria of stem cells: Stem cell exhaustion in hutchinson-gilford progeria syndrome. The Journal of Gerontology. 2007;62A(1):3-8.

Koshimizu E, Imamura S, Qi J, et al. Embryonic senescence and laminopathies in a progeroid zebrafish model. PLoS One. 2011;6(3).

Kudlow BA, Kennedy BK, Monnat,Raymond J.,,Jr. Werner and hutchinson-gilford progeria syndromes: Mechanistic basis of human progeroid diseases. Nature Reviews.Molecular Cell Biology. 2007;8 (5):394-404.

Liu Q, Kim DI, Syme J, LuValle P, Burke B, Roux KJ. Dynamics of lamin-A processing following precursor accumulation. PLoS One. 2010;5(5).

Mohamed Riyaz S, Jayachandran S. Progeria. Indian Journal of Dental Research. 2009;20(4):508-10.

Mounkes L, Kozlov S, Burke B, Stewart CL. The Laminopathies: nuclear structure meets disease. Curr Opin Genet Dev. 2003;13:223-230.

Neelam S, Krishna M, Semwal BC, Shravan P, Kuldeep S, Deepak S. Progeria: A Review. International Journal of Pharmaceutical Sciences Review and Research. 2012;14(1):4449.

Osorio FG, Obaya ÁJ, López-otín C, Freije JM, P. Accelerated ageing: From mechanism to therapy through animal models.Transgenic Res. 2009;18(1):7-15.

Rakha P, Gupta A, Dhingra G, Nagpal M. Hutchinson-- Gilford Progeria Syndrome: A Review. Der Pharmacia Sinica [serial online]. February 2011;2(1):110-117.

Scaffidi P, Misteli T. Good news in the nuclear envelope: Loss of lamin A might be a gain. J Clin Invest. 2006;116(3):632-4.

Sousa SF, Fernandes PA, Ramos MJ. Farnesyltransferase inhibitors: A detailed chemical view on an elusive biological problem. Curr Med Chem. 2008;15(15):1478-92.

Yang SH, Meta M, Qiao X, Frost D, al e. A farnesyltransferase inhibitor improves disease phenotypes in mice with a hutchinson-gilford progeria syndrome mutation. J Clin Invest. 2006;116(8):2115-21.

Zaremba-czogalla M, Dubiska-magiera M, Rzepecki R. Laminopathies: The molecular background of the disease and the prospects for its treatment. Cell Mol Biol Lett. 2011;16(1):114-48.