

An Updated Review On Hutchinson-Gilford Progeria Syndrome

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Abstract:

In 1886 Jonathan Hutchinson first identified the disease “Progeria” and thereafter by Hastings Gildford in 1897. It was later renamed as Hutchinson-Gilford Progeria syndrome (HGPS). HGPS is a genetic disorder identified by accelerated aging immediately after birth in the first year of life. Clinical trials by using different drugs either alone or in combination are under progress. Recently it was discovered that rapamycin is efficient in not only clearing defective protein progerin but also inhibits geroconversion process. Another drug resveratrol improved lifespan of patients. Accumulation of progerin activates NF-κB pathway which produces inflammatory cytokines leading to inflammation of progeroid mice, this pathway was inhibited by simultaneous use of statins, aminobisphosphonates and Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Recently, a new technology named CRISPR/Cas system permits to edit genome at specific loci which is permanent. The combination of non-integrating transient vectors with CRISPR/Cas constructs proven effective for the treatment of HGPS. This review summarizes recent updates made in understanding of HGPS and focuses on recent developments in research of HGPS in terms of physiological processes and drug discovery.

Keywords: HGPS, Lamins, FTIs, Rapamycin, Resveratrol, Crispr Constructs

INTRODUCTION

The disease manifested with aging phenotype in the first year of life is identified as HGPS [1, 2]. Dr. Hastings Gilford based on the appearance of old age characteristics derived the term progeria from words pro (before) and geron (old person) of Greek origin [3, 4]. The conspicuous features of the disease include the general resemblance of patients to aged individuals and aging-associated symptoms which include recognizable superficial veins, short stature, alopecia, lipodystrophy, abnormal contractions of muscle in joints, the progressive cardiovascular disease resembling atherosclerosis and most of them die due to myocardial infarction and heart attacks [5]. However, there is no retardation in mental growth and intellectual capabilities. For more than 100 years HGPS molecular mechanism was not clearly understood. Disease secrecy was resolved by the identification of the gene named as LMNA, responsible for this fatal autosomal genetic disorder. Patrilineal allele mutation of LMNA gene was

found in 90% HGPS affected children. When thymine is substituted by cytosine, processing of mRNA is altered, resulting in the synthesis of shortened, farnesylated and incompletely processed protein named as “progerin”. Protein progerin is an abnormal prelamin-A which on accumulation leads to the development of disease related abnormalities [6, 7]. The discovery of the genetic basis of the disease attracted many scientists from academics and industries to resolve its mystery and the first ever clinical trial was started in 2007 and successfully completed in 2009 [8]. Thereafter a mini trial of one month duration was conducted in March-2009 followed by a third trial started in Aug-2009, which is under progress to till date [9].

EPIDEMIOLOGY

Since most of the HGPS cases remain undiagnosed prevalence rate was found to be 1 in 4 or 8 million births, with 134 known cases all around the world and 1.2:1 is the male to female ratio. Age at which the disease can be diagnosed is 2.9 years and diagnosis is clear as the

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Figure 1: Incidence of children with HGPS around the world as of Dec-2015. Adapted with permission and courtesy of the Progeria Research foundation www.progeriaresearch.org

affected children shows similar symptoms of disease progression. Incidence is considered as sporadic because it is uniform all around the world, showing no geographical, gender and ethnic susceptibility. According to Progeria Research Foundation (PRF) report of Dec-2015, 134 children were diagnosed with HGPS (Fig 1) [10, 11]. HGPS affected children have no difference in weight and appearance at the time of birth, but symptoms appear in the first year of life which becomes prominent with age and most of them die due to myocardial infarction and heart attacks. 13.5 years is found to be average life span. According to a report only one patient survived up to 45 years of age. (Fig 2) [12].

CLINICAL FEATURES OF HGPS

The first noticeable signs is bluish discoloration of the skin surrounding mouth and a vein appearing on the nasal bridge. Most of the children are identified with alopecia, osteolysis, endocrine impairment and auditory

dysfunction within the age group of 1st to 3rd year of life [13].

Physical characteristics

Abnormalities of the skin and scalp such as prominent scalp veins and scleroderma are transient features of HGPS. Physical manifestations also include inelastic, indurated, shiny, frickle like hyper-pigmented skin, progressive loss of eye lashes and eyebrows. Areas of skin particularly over the hands and feet may appear aged. Body hairs are completely absent. Growth rate is significantly disturbed with weight than height. Mean weight of patients was found to be 14.54kgs. Patients exhibit high pitched voice and have short stature [14, 15]. Loss of intra orbital fat makes eyes to look protuberant and ears also appears protruding without lobes. Micrognathia in the chin and the point of nose becomes flattened in HGPS [2].

Abnormalities of Musculoskeletal system

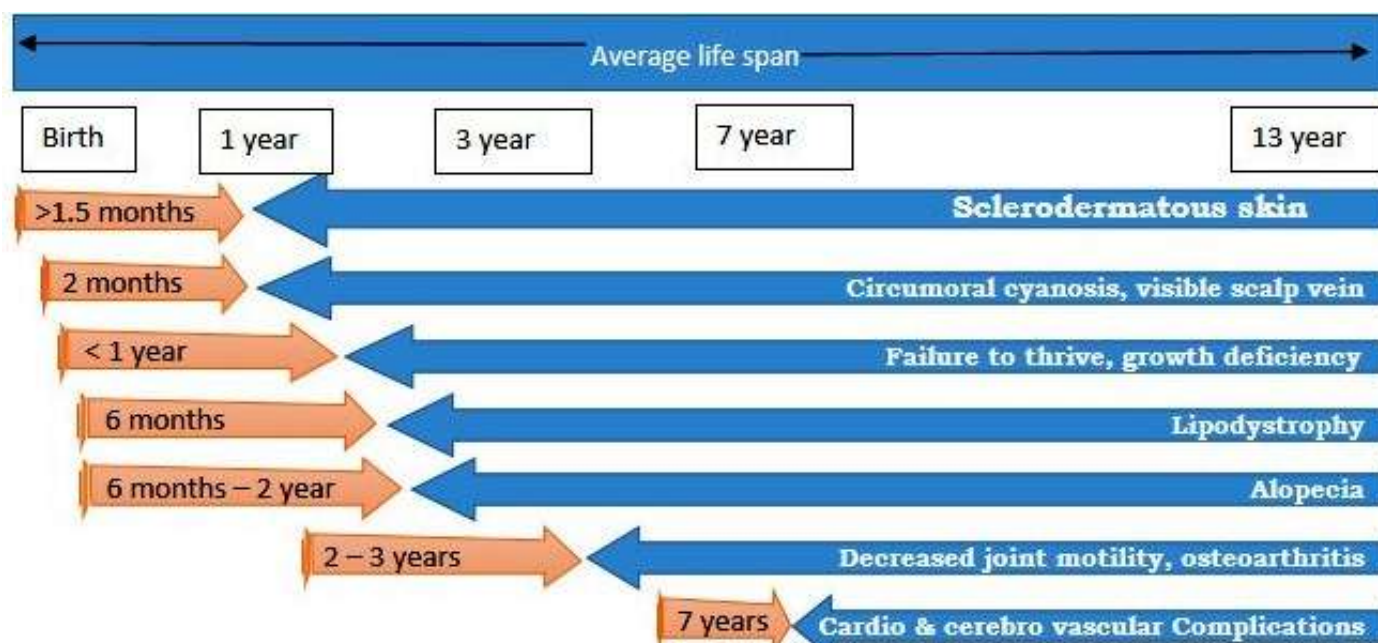


Figure 2: Common clinical signs of HGPS and typical time of presentation. This work is adapted from “Accelerated Aging in Patients with Hutchinson-Gilford Progeria Syndrome: Clinical Signs, Molecular Causes, Treatments, and Insights into the Aging Process” and attributed to Parreno, J., Curz, A. V., 2011. UBCMJ 3(1): 8-12, and it is licensed under Creative Common Attribution License (CCAL) 2.5, and full terms can be found at <http://creativecommons.org/licenses/by/2.5/legalcode>

Characteristic musculoskeletal manifestations include pear shaped thorax, weaken and atrophic clavicles, narrow shoulders, joint contractures in limbs, bending and dislocation of hip joints presenting an appearance of “horse riding” stance (increased distance between the thighs). Most of the bones undergo osteolysis which increases the risk of hip joint dislocation and also humerus fracture [16]. Distinguishing features which appeared early include thin lips, narrowing of the nasal bridge, lagophthalmos, subsided lower jaw. Final confirmation of the disease is based on identification of clinical features and molecular genetic testing [17].

Cardiovascular system

Cardiovascular complications arise within the first decade of life and mainly responsible for mortality. Progressive vasculopathy initiated by calcified arterial lesions followed by vessel plaques, hypertension, angina, myocardial fibrosis, interstitial fibrosis, and deposition of calcium in different valves like aortic and mitral. In

addition, cerebrovascular complications such as hemiplegia, subdural hematoma, and seizures have been reported [18].

Other anomalies

Secondary sexual characters are very unusual and breast development is virtually absent. Dystrophic nails, Hyperplastic nipples, Anodontia, hypodontia, malocclusion, impairment of teeth arrangement and development, increased prothrombin time, hypertension, loss of hearing, hyperphosphatemia, and increased platelet counts are reported. HGPS patients remain reserved because of their appearance among strangers and they display affection and good social interaction in the presence of friends [12].

PATHOPHYSIOLOGY

HGPS disease is characterized by mutations of LMNA gene that produces progerin [8] which on accumulation contributes to the risk of atherosclerosis and increased susceptibility to mechanical strain in vascular cells.

Increased susceptibility triggers the death of the cell and in 90% of patients atherosclerosis of arteries of heart and brain may occur due to inflammation [19]. Decrease in the expression of prelamin-A in organs such as brain results in dementia and mental deterioration [20]. In Acute phase biopsy analysis of sclerodermatous skin reveal normal epidermis, thickened corium while later stage biopsies showed decreased cellularity, thickened dermis with thick mature collagen bundles and atrophic adipose tissue [21]. DNA repair mechanism becomes

inefficient due to slowed repair kinetics and decreased DNA damage response factors to sites of damage [22]. Unlike in normal physiological ageing, thrombocytosis and extended clotting time have been reported in HGPS patients. Other motifs for mortality in HGPS patients are malnutrition conditions like loss of morbidity, marasmus and inanition [23].

Molecular background of HGPS

HGPS is classified into a group of systemic laminopathies

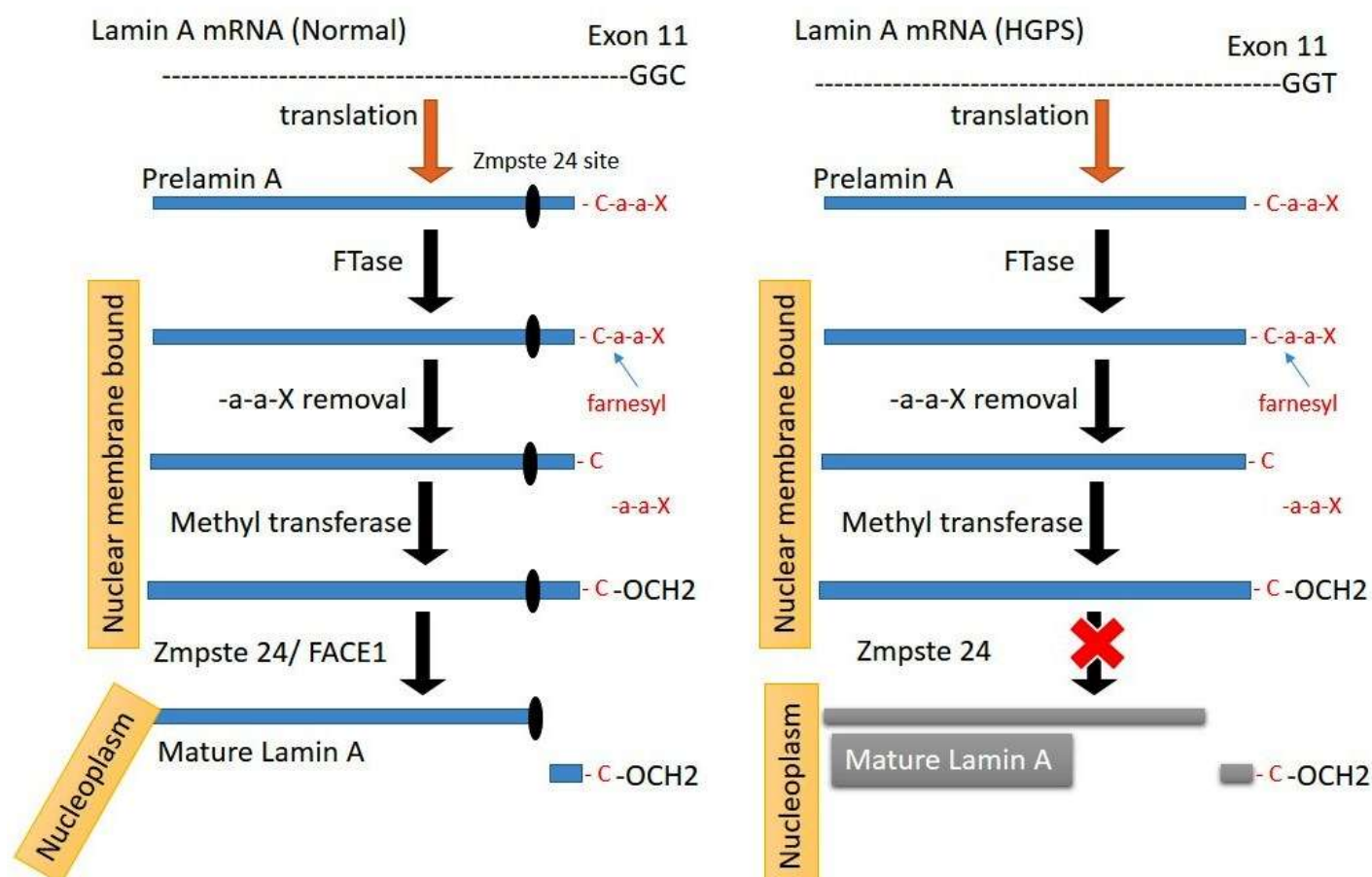


Figure 3: Normal processing of lamin A from mRNA to mature lamin A: Normal lamin A mRNA is translated to prelamin-A which is farnesylated resulting in anchoring to the inner membrane of nucleus. Zmpste24 cleavage of amino acids results in release from the nuclear membrane and accumulation in to the nucleoplasm. Processing of lamin A in patients with HGPS. Mutated lamin-A mRNA is translated to prelamin-A which does not contain Zmpste24/FACE1 cleavage site. Farnesylated prelamin-A then anchors to the inner membrane of nucleus. Lack of Zmpste24 cleavage of terminal amino acids results in deficiency of mature lamin A. This is adapted from "Accelerated Aging in Patients with Hutchinson-Gilford Progeria Syndrome: Clinical Signs, Molecular Causes, Treatments, and Insights into the Aging Process" and attributed to Parreno, J., Curz, A. V., 2011. UBCMJ 3(1): 8-12, and it is licensed under CCAL 2.5, and full terms can be found at <http://creativecommons.org/licenses/by/2.5/legalcode>

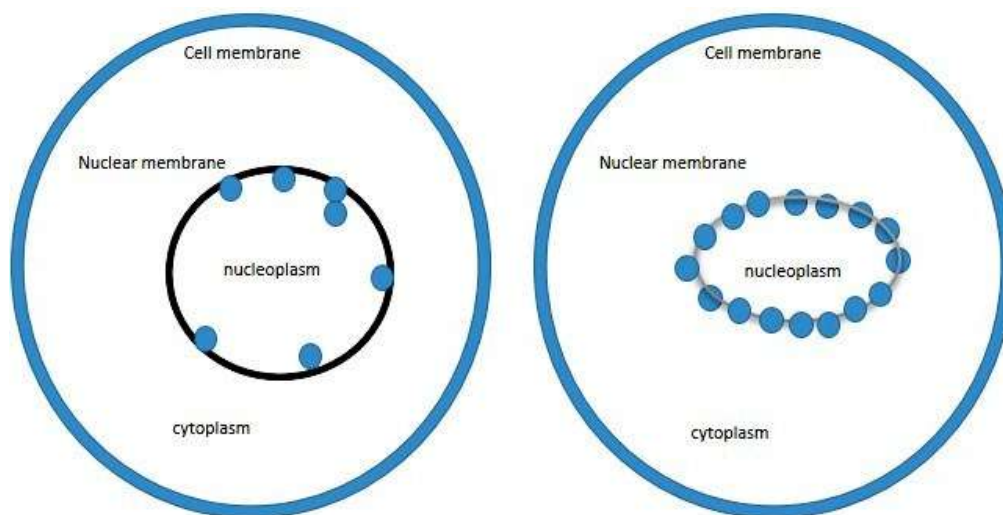


Figure 4: In normal subjects, prelamin-A is cleaved by Zmpste24/FACE1 to generate mature lamin A which accumulates in nucleoplasm. In HGPS patient prelamin-A remains farnesylated, accumulates at the inner membrane of the nucleus, and results in distorted nuclei. This is taken from “Accelerated Aging in Patients with Hutchinson-Gilford Progeria Syndrome: Clinical Signs, Molecular Causes, Treatments, and Insights into the Aging Process” and attributed to Parreno, J., Curz, A. V., 2011. UBCMJ 3(1): 8-12, and it is licensed under CCAL 2.5, and full terms can be found at <http://creativecommons.org/licenses/by/2.5/legalcode>

which also includes Werner’s syndrome. HGPS gene LMNA along with other 80 known genes was discovered to lie on 4.82 Mb region of chromosome 1q by a group working at National Human Genome Research Institute in Maryland [24].

Two types of lamins forming inner layer of nuclear envelope are A-type and B-type. These lamins are key protein components of the nuclear lamina. Defects in B-type lamin is lethal as it majorly involved in gastrulation and development, whereas laminopathies are due to defects in A-type lamin. Lamin A protein contains 664 amino acids and is typically synthesized as a precursor molecule called prelamin-A which contains a C terminal cysteine-aliphatic-aliphatic-any amino acid box (CAAX box) motif which is subjected to farnesylation at Cys residue a process of C-terminal lipidification. In CAAX box farnesyl group addition to a cystine residue via farnesyltransferase is termed as Farnesylation. Later this precursor molecule prelamin-A undergoes proteolytic cleavages in two ways, first cleavage occurs at the C-terminal, the –aaX tripeptide is enzymatically released. In the next step Methyl transferase adds methyl group

to the remaining farnesylcysteine [25]. In the final step, mature lamin is formed by the removal of 15 amino acids end present on prelamin-A by zinc metalloproteinase [26]. Synthesis and repair of DNA, expression of gene and organization of chromatin are controlled by nuclear lamins [27].

There is no modification of the farnesyl group in mature A-type lamin (Fig 3). Occurrence of disease is mainly due to LMNA gene (band 1q21.1-1q21.3) mutation. Prelamin-A is synthesized due to inhibition of mature lamin-A production, which is outcome of zinc metalloproteinase, STE24 (Zmpste24) gene deletion. In exon 11 and at location 1824 about 90 % of HGPS affected patients have cytosine to thymine (GGC to GGT) single point mutation [28]. This heterozygous point mutation produces a molecule with 150 base pairs which is shorter than normal. Zmpste24 cleavage sites are present among the 50 amino acids, which are not translated. Farnesylated (retaining CAAX motif) prelamin-A attaches to an inner layer of nuclear envelope and forms a mutant protein “progerin”. The second cleavage site is absent in the progerin due to this

prenyl group of the progerin is associated to nuclear envelope. HGPS patients have blebbed and distorted nucleus with a thick nuclear lamin-A (Fig 4) [29]. Moulson and others suggested, higher the concentration of the progerin more severe is the disease.

DIAGNOSTIC FEATURES

Clinical and radiographic features are to be assessed as the part of diagnostic features in determining HGPS.

Blood and urine analysis

Hypoalphalipoproteinemia, increased level of hyaluronic acid with no change in total cholesterol and LDL are observed in HGPS affected patients [30].

Clinical analysis

Macrocephaly, micrognathia, thinning and resorption of the distal clavicles are characteristic radiological abnormalities in HGPS. Sclerodermatous skin and lipodystrophy are attributes observed in patients affected with HGPS. One of the hallmarks is loss of bone from finger and toes distal phalanges. Protruding eyes with prominent cranial veins on the scalp are heightened by alopecia [31].

Lmna mutation test

PRF, in association with a Clinical Laboratory Improvement Amendments (CLIA) approved diagnostics centers, are pleased to provide a DNA-based, investigative test for children suspected of having HGPS. After an intense scientific search, the gene for HGPS was found on April 2003 in the PRF Genetics Consortium.

Diagnosis of the progeria is done by genetic test of the causative mutation. As a de novo mutation in codon G6084 appears to be the reason of HGPS, screening for this mutation assist in reducing the risk of misdiagnosis. However prognostic screening is impractical due to the sporadic nature of the mutation, hence a risk factor in children cannot be determined. The concerns of parents with previously affected children about the recurrence in future pregnancies can be addressed through genetic testing [32].

TREATMENT

In 1998, Dr. Leslie Gordon launched The PRF which functions to raise awareness, educate and help doctors, families, researchers and the public about HGPS. In addition, PRF grant funds for medical research and carries out research-related programs to understand the mechanism involved in the origin and treatment of the disease. PRF in combination with National Institutes of Health reveal that the cause of Progeria, a mutation in the LMNA gene. First treatment was started with Lonafarnib in September 2012. Over \$6.7 million of the fund was released by PRF for HGPS related research projects [33].

Farnesyl Transferase Inhibitors (FTIs), Statins and Aminobisphosphonates:

After the discovery of the gene, within a short span of 5 years first human clinical trial was started. HGPS is incurable aside from symptomatic treatment therapy. Improvement was observed in individuals with HGPS on treatment with growth and nutritional hormones. The main goal of this therapy is to decrease the requirement of energy and to increase weight and height of HGPS patients. The drug repurposing method was implemented which utilizes FTIs previously developed as an anticancer drug. According to the results of preclinical studies FTIs were found to decrease the severity of disease. These drugs mainly act by blocking farnesylation of progerin and thereby suppressing the progression of the disease. FTIs inhibits farnesyl protein transferase that directs farnesylation of prelamin-A containing C-terminal CAAX motif such that all subsequent processing reactions are inhibited. Positive figures in vascular stiffness, body weight and bone mass among 25 patients have been reported upon treating with FTI Lonafarnib for 2 years. Among these 25 patients rate of weight gain are observed as 50% increase (in 9 patients), 50% decrease (in 6 patients) and remained stable (in 10 patients). Based on these results it was concluded that lonafarnib ameliorates bone structure, audiological status and vascular stiffness [34]. FTIs are

acting to prevent early onset and delayed the advancement of cardiovascular disease [35]. Shortcomings to the lonafarnib treatment were reported such as blocking farnesylation of B1 and B2 lamin which may result in more severe damage to the nuclear lamina. In absence of farnesyl protein transferase, prelamin-A is processed by geranylgeranylation an alternative route of prenylation. As a result progerin levels are increased, thus reducing the efficacy of FTIs in the treatment. This modification could be blocked by inhibiting the production of both geranyl-geranyl and farnesyl precursors by statins and aminobisphosphonates. This result explains that FTI treatment simply increased lifespan in a mouse model and prompted several ongoing therapeutic trials. In these clinical trials FTIs are combined with statins eg: pravastatin and aminobisphosphonates eg: zoledronic acid (Fig 5) which proved to be a powerful continual approach for enhancing disease treatment [36].

Rapamycin

Based on this drug-repurposing approach another candidate rapamycin or everolimus (a macrolide antibiotic) is used for the treatment. Rapamycin act by clearing progerin and blocks the development of structural defects in the nucleus, delays senescence and improves the lifespan of affected cells. It also act by suppressing atherosclerosis and geroconversion (Fig 6) (conversion from quiescence to senescence) [37,38]. PRF is promoting two-drug combination of FTIs plus rapamycin. Rapamycin can be given easily to children with HGPS because it requires fewer blood draws to measure drug levels. While FTIs may inhibit progerin from developing, whereas toxic progerin is cleared from cells by the action of rapamycin. Thus, with rapamycin targeting a different pathway than FTIs, the combination may work as “one-two punch” to Progeria proving to be a better treatment than FTIs on its own [39, 40].

Resveratrol

Another compound of interest is resveratrol, which act as SIRT1 (SIRTUIN-1) activator that interacts with lamin A.

In HGPS mouse model due to the accumulation of defective protein progerin, SIRT1 is weakly associated with the nuclear matrix. As a result deacetylase activity of SIRT1 is decreased, leading to speedy destruction of adult stem cells. Lifespan and cellular phenotypes were improved in the HGPS mouse model after treatment with resveratrol [41].

Salicylates

In the HGPS patients accumulation of progerin triggers nuclear stress pathway involving the activation of two proteins, namely ATM (Ataxia-Telangiectasia-Mutated Protein Kinase) and NEMO (IKK γ and IKK Regulatory Subunit). Activated NEMO moves in to the nucleus and is phosphorylated by ATM. This phosphorylated NEMO moves out of the nucleus where it acts to trigger cytoplasmic IKK complex and finally NF- κ B whose activation promotes the synthesis of senescence associated inflammatory cytokines like IL-6, CXCL1 and TNF- α . These cytokines cause systemic inflammation, which will affect the distant cells and tissues and decreases their lifespan. According to Osorio, Sodium salicylate treatment efficiently blocks NF- κ B activation in Zmpste24-deficient mice & extends life span and prevents HGPS features of Zmpste24-deficient mice [42].

RNA Therapy

HGPS mainly results due to activation of alternative pre-mRNA splice site. Scaffidi and Misteli, in 2005, showed the effect of antisense oligonucleotide in inhibiting the pre-mRNA splice site of HGPS fibroblasts [43]. Osorio et al., in 2011 developed a new HGPS mouse model which was characterized by the symptoms of human HGPS patients and they also supported the efficacy of antisense oligonucleotides by inhibiting the accumulation of defective protein progerin and its associated abnormalities like decreased life span. Moreover, it was confirmed by improved body weight and extended lifespan of HGPS mouse model [44]. Huang et al., followed an alternative approach to eliminate the progerin mRNA using Small interfering RNA (siRNA)-based methods [45].

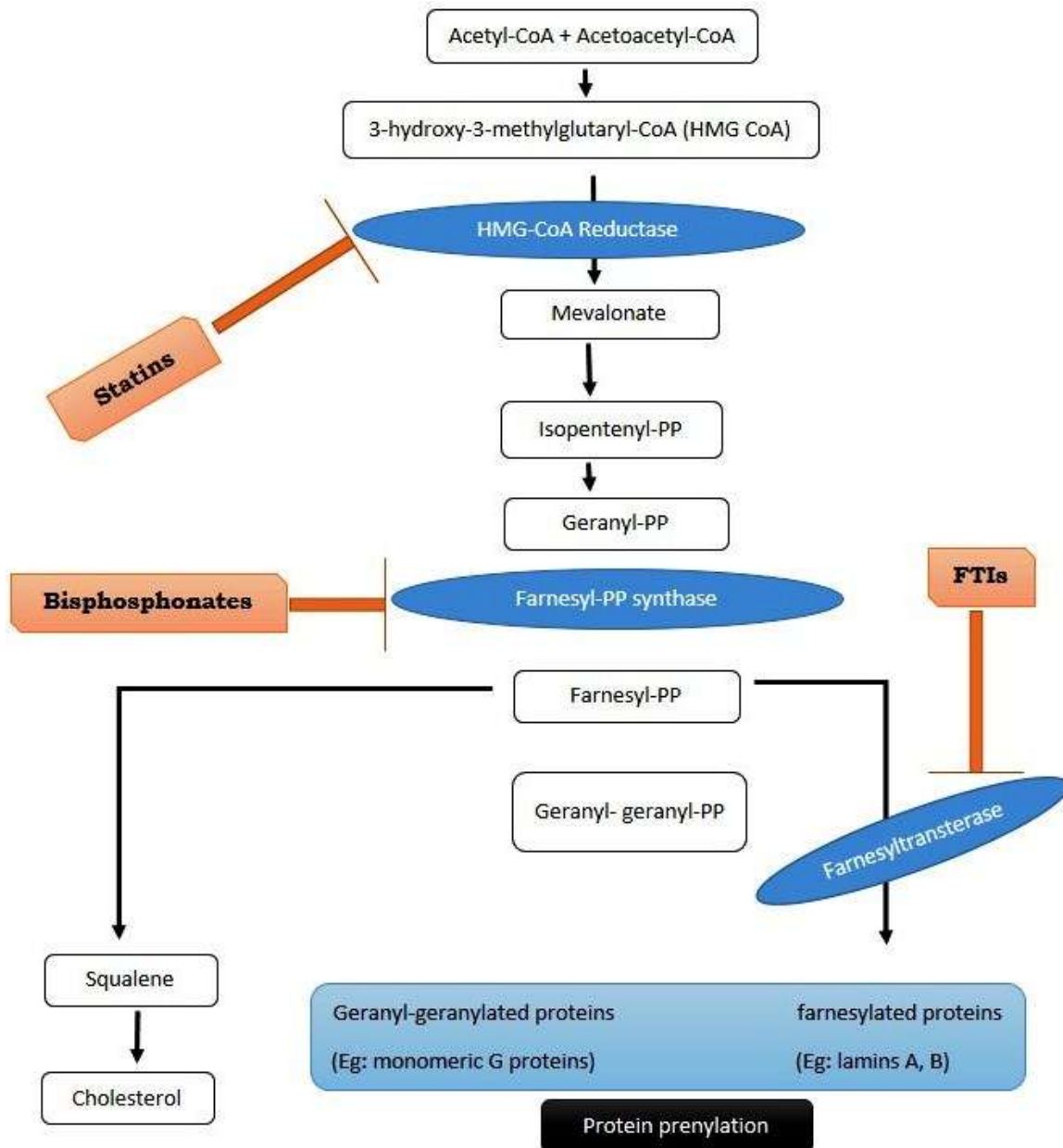


Figure 5: Statins and FTIs for the treatment possibilities of HGPS. This is taken from: <http://www.intechopen.com/books/genetic-disorders/hutchinson-gilford-progeria-syndrome>, attributed to Baek, J., McKenna, T., Eriksson, M., 2013, and it is licensed under CCAL 3.0, and full terms can be found at <http://creativecommons.org/licenses/by/3.0/legalcode>. PP stands for pyrophosphate.

Stem Cell Treatment

Based on the advancements in reprogramming technology, it was found that somatic cells derived from human induced Pluripotent Stem Cells (iPSCs) are able to produce in-vitro HGPS disease model [46]. Stem cell dysfunction will lead to HGPS alterations [47, 48]. In vitro, progerin affects the differentiation and

multipotency of the human mesenchymal stem cells, and HGPS patient-derived iPSCs exhibit defects in differentiation [49]. Proliferative efficiency of epidermal stem cell was reduced in HGPS-related cellular model [50]. Mechanism of wound healing was impaired and population of epidermal adult stem cells was decreased in an inducible HGPS mouse model [51]. Zhang et al in 2011 derived neural cell lineage from iPSCs obtained

from HGPS patients to evaluate the expression of lamin-A in these cells [52]. Later in 2012, it was found that mi-R9 a type of micro-RNA regulates the expression of lamin-A in neural cells [23]. Nissan et al., for the first time proposed the pathophysiological relation of mi-R9 and neural cells. They found that decreased expression of mi-R9 in neural cells protected them from progerin accumulation related cell abnormalities [53]. Blondel et al., derived mesodermal stem cells (MSCs) from HGPS patient's iPSCs, showed the abnormalities related to progeria. MSCs treatment with three different categories of drugs, namely FTIs, rapamycin and combination of pravastatin with zoledronate relieved all the cellular abnormalities related to progeria. In addition to this, the use of different drug combinations has not shown any beneficial results when compared to individual drug treatments. Thus iPSCs derived cells function as a best approach to evaluate the pathophysiology of the disease, mechanism of action of drug and comparing the action of different drug combinations [54].

Gene Therapy Approaches

Gene therapy mainly aims to manipulate the genome

and revert their phenotype to wild type. In bacteria and archaea CRISPR/Cas (Clustered-Regulatory-Interspaced Short Palindromic Repeats) system was discovered as a tool for genome editing. This tool helps to manipulate the pathogenic mutation using transient viral vectors such as adenoviral derived vectors [55]. CRISPR-Cas system is of 3 types, out of this type II is transformed into a high efficient genome editing tool [56]. Type II involves 3 components CRISPR RNA (cr RNA), a transactivating CRISPR RNA (tracr RNA) and the Cas-9 protein. Portions of the viral DNA is inserted into bacterial genomic CRISPR loci. Inserted sequence is transcribed into specific cr RNA. Double stranded breaks are produced by Cas-9 double stranded DNA endonuclease which in turn guided by Trace RNA and sequence specific cr RNA [57]. DNA repair mechanism functions to repair these breaks during which small insertions called as indels may occur. These indels alter open reading frame and causes an early truncation of the proteins [58].

For efficient transduction viral vector is used. Adenoviral derived vectors are efficient for carrying CRISPR/Cas constructs. Therefore, this technology was employed for the treatment of HGPS caused by negative mutation [59].

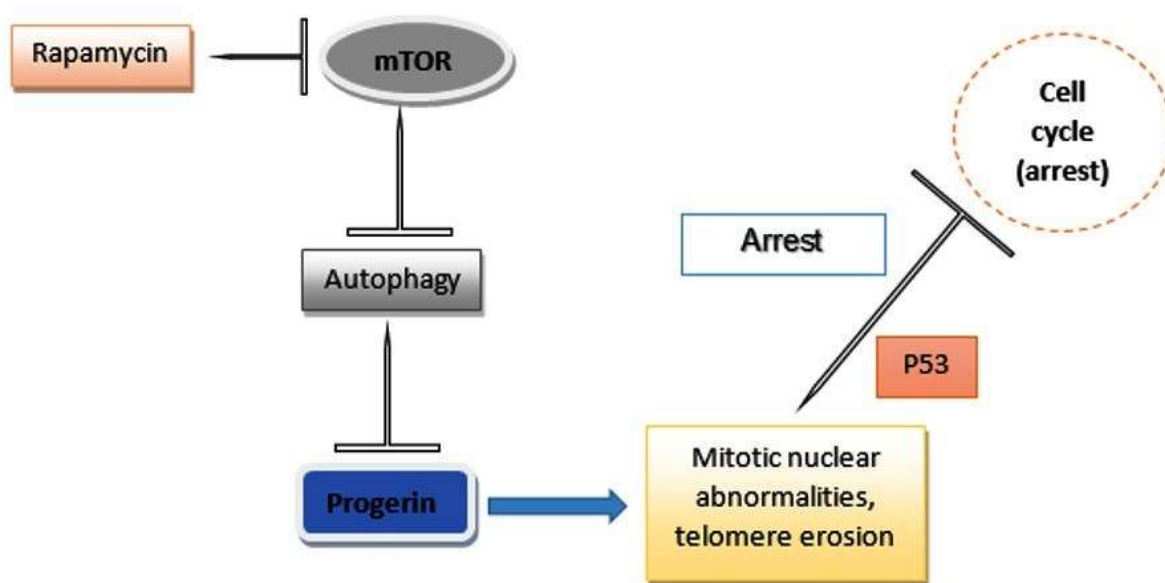


Figure 6: Replicative limit induced by Progerin in HGPS cells Rapamycin prevents telomere erosion and cell cycle arrest by decreasing the levels of progerin. This is adapted from work "Progeria, rapamycin and normal aging: recent breakthrough" attributed to Blagosklonny, M. V., 2011. Aging 3(7): 685-691. It is licensed under CCAL.

When genome is edited in the mutated locus non-homologous end joining mechanism is activated which will produce a truncated form of progerin that highly resembles the wild type unfarnesylated mature lamin A [60].

CONCLUSION

Despite being chronicled more than 100 years ago, limited knowledge on the root cause of HGPS has been attributed to low incidence rate and sporadic nature of the disorder. HGPS is due to LMNA gene negative mutation leading to accumulation of progerin. Prior to gene identification, treatment was limited to, nutritional or growth therapy. Notably, over the past few years, many achievements in research led to the development of potential strategies for viable treatment options. FTIs implemented as per drug repurposing method suppress development of HGPS phenotype by blocking farnesylation of progerin. Drugs such as NSAIDs, are also being clinically evaluated for treatment as they block the NF- κ B signaling hyper activation noticed in progeroid cells. Nonetheless, the drugs that are undergoing clinical trials lack the efficacy to target mysterious splice site. Further research is crucial in the development of alternative treatment strategies. Detailed study of laminopathies may also advance our insight in the process of ageing.

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