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Mini Review

Hutchinson-Gilford Progeria Syndrome: Premature Aging

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Abstract

Hutchinson–Gilford Progeria Syndrome (HGPS) is a rare fetal disorder that causes children to age faster than normal. This disorder results from a point mutation in the LMNA gene resulting in production of progeria, an abnormal form of Lamin A. Progeria damages the nuclear structure. As a result, cells in HGPS patients experience DNA damage, altered chromatin structure, and epigenetic dysregulation. Children with HGPS typically experience hair loss, thin skin and early heart disease. While there is still no cure for this disease, newer techniques such as RNA based treatments show encouraging progress. Studying HGPS continues to deepen our understanding of the molecular pathway involved both pathological and normal aging.

Introduction

Hutchinson Gilford Progeria syndrome (HGPS) is a rare, genetic disorder named after two researchers, Dr. Jonathan Hutchinson and Dr. Hastings Gilford. Hutchinson Gilford Progeria syndrome (HGPS) is characterized by rapid aging, results in early wrinkling appearance of the skin in children, growth failure, loss of body fat, hair loss, and cardiovascular diseases, HGPS affects 1 in 4-8 million people worldwide, both sexes equally and all races [1]. Despot being a rare mutation, HGPS has gained significant attention because studying it on one hand help understand the disorder at other hand the fundamental process of normal human again. HGPS is caused by an autosomal dominant point mutation in the LMNA gene located on chromosome 1q22. This gene encodes for structural proteins Lamin A and Lamin C. Lamin A plays an important role in regulating chromatin organization. The mutation creates a cryptic splice site, result in misshaped version of Lamin A known as progeria. As a result, progeria remains permanently anchored to the nuclear envelope, disturbing the organization of chromatin. Clinically, Children affected by HGPS have a normal appearance during their early childhood (Infancy) and begin to experience growth delay at approximately 9 to 24 months of age. Common features include small jaws, large head relative to body mass, and large eyes. Heart problems, especially atherosclerosis, are the main cause of death among children with this disorder and most patients die in their teenage years. This review aims to summarize current knowledge on HGPS, focusing on different aspects of Hutchinson Gilford Progeria syndrome (HGPS) including genetic and molecular basis, cellular and physical consequences, clinical features and diagnosis, and current and emerging therapeutic strategies. By reviewing and highlighting both progress and challenges of this again syndrome we aim to better understand it.

Result

Genetic basis of HGPS

HGPS originates from a point mutation in axon 11 of the LMNA gene, a Cytosine to Thymine replacement. This mutation is a silent mutation that results in a cryptic splice site, leading to the deletion of 150 nucleotides in the pre-Lamin A mRNA. This produces a misshaped form of a Lamin A called progeria, which lacks the site for ZMPSTE24-mediated cleavage, prevent the removal of the farnesyl group from C-terminal of Lamin A [2]. The mutation is an autosomal dominant, but affected children often inherit the mutation de novo, without family history. This explains the lack of familial patterns observed in HGPS cases.

Molecular mechanisms

Lamin A and Lamin B1 play an important role for nuclear shape and stability. Hutchinson-Gilford progeria syndrome (HGPS) results in loss of smooth muscle cells (SMCs), cause DNA damage, cell death, and nuclear membrane ruptures, which causes a decrease in level of Lamin B1. [3]. Lamin B1 is a major protein from nuclear lamina that helps maintain nuclear shape, stability, and organization of heterochromatin. In individual with HGPS, progeria build up at the nuclear envelope because it remains permanently forensicated, causing nuclear blebbing. This abnormal progeria led to a disruption in interferes of anchoring chromatin to the nuclear membrane, lead to a disruption of DNA organization and. Production of Progeria result in loss of heterochromatin, cause a reduction in H3K27me3 and H3K9me3 modifications. These changes result in abnormal gene activity of the LMNA gene, which causes silence to a normally repressed gene. Disrupting the connection between nuclear lamina and DNA negatively alters gen regulation, causing cells to stop dividing and promoting faster cellular aging.

DNA Damage and Telomere Abnormalities

Nuclei accumulation of damaged DNA in HGPS shows increase in activation of DNA damage response (DDR) markers. The cell also has unstable chromosomes because they have trouble repairing DNA double strand breaks this result in telomere shortening and dysfunction [4]. Important repair protein is Rad51, in HGPS cells this protein does not move to DNA breaks in the right way and results in less effective repair. At the same time, 53BP1 builds up as DNA-damage foci, indication sustained DNA damage signaling. Along with faster shortening of telomeres, these problems cause instability in the genome and lead to early cell aging. These molecular problems lead to several issues in the cells. HGPS cells age faster and undergo early growth arrest compared to normal cells, releasing molecules that negatively affect and damage nearby tissues.

Clinical Feature

Patients with Hutchinson-Gilford Progeria Syndrome (HGPS) born without noticeable abnormalities, then begin exhibiting features of accelerated age around 18-24 months of age. Common characteristics include craniofacial abnormalities such as prominent eyes, thin nose, and small jaw- along with thin skin, loss of body fat and bone problems such as stiffness in joint or hip dislocation. Cardiovascular complication led to About 80% of death among HGPS patients [5].

Current and Future Treatment

Different treatments strategies are being tested for Hutchinson-Gilford Progeria Syndrome (HGPS). Farnesyltransferase inhibitor (FTIs) drugs such as lonafarnib work by blocking the farnesylation, helps reduce production of progeria and toxicity. Lonafarbin is an FDA approval drug that helps improve HGPS sympthoms. FTI are small molecules that would reversibly bind to the binding site of farnesyltransferase [1]. Moldes treated with FTIs, show weight improvement, and increase in lifespan. RNA based therapies using antisense oligonucleotides (ASO) lead to reduction of progerin levels by targeting LMNA mRNA and show potential in correcting nuclear defects in laboratory studies. Gene-editing methods like CRISPR-Cas9 aim to correct the LMNA mutation or remove the cryptic splice site [6]. Furthermore, cellular and supportive therapies such as mesenchymal stem cells treatment, may support vascular and skeletal health, while heart monitoring, balanced nutrition, and physiotherapy help to improve overall health of the patient.

Discussion

Hutchinson–Gilford Progeria Syndrome (HGPS) provide important model for studying fundamental processes of nuclear organization. Identification of progerin production as the toxic protein responsible to HGPS disease shown how a single base mutation in the LMNA gene can result in cellular dysfunction and accelerated aging. While drugs like lonafarnib can help with symptoms and extend life spam and prevent cardiovascular diseases but unfortunately do not cure the disease [1]. Meanwhile, other treatments approach like RNA base and gene editing therapies are aimed at targeting the root genetic defects. However, these strategies still need further work to overcome challenges such as long-term effectiveness, safe delivery, and potential side effects. In addition, studying HGPS helps extend researchers' understanding of biology of normal aging. Progerin, the protein that causes premature aging in HGPS, can also be found in healthy cells. Small amounts of progerin build up slowly in healthy cells over time. Consequently, studying HGPS could reveal how the same processes cause common age-related problems, such as heart disease, tissue damage, and organ decline. This research may help both people with HGPS and older adults.

Conclusion

Hutchinson–Gilford Progeria Syndrome (HGPS) is a rare genetic disorder that provides important details of mechanisms of aging. HGPS is caused by a spontaneous de novo point mutation in the LMNA gene in codon 608 of exon 11 on chromosome 1result in production of progerin [7]. Progerin is formed by misshaped nuclear envelop and disorganized chromatin, leads to DNA damage and result in premature cellular senescence. While children with HGPS show no symptoms at birth, they start to show signs of rapid aging, including hair and body fat loss, joint stiffness and growth failure usually within 9-24 months after birth. Cardiovascular problems such as arterial stiffness are the primary cause of death among individual with HGPS. Advances in understanding how progerin works have helped to develop several different therapeutic strategies. A Farnesyltransferase inhibitors (FTIs) drug such as lonafarnib can improve the symptoms and increase lifespan, RNA based methods aim to target the root genetic cause of the disease and lower progerin level. Research on HGPS provides insight into normal aging processes, as low levels of progerin also accumulate in healthy individuals over time. Studying HGPS may reveal mechanisms under lying cardiovascular disease, tissue degeneration and other age-related conditions. Future studies should focus on improving methods that enhance long-term effectiveness therapies like RNA based and gene editing and exploring how progerin influences physical aging. In summary, HGPS not only highlights the damaging effects of progerin accumulation on cellular function and aging but also serve as a key model to study and understand normal aging process itself. Ongoing progress in molecular biology and genetic technologies brings hope for more effective and longer lasting treatments. The knowledge gained from HGPS research could benefit both children with HGPS and everyone affected by age related conditions [8-25].

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