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Progeria Syndrome Unveiled: A Scientific Odyssey into Premature Aging Mechanisms and Therapeutic Frontiers

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Abstract

Progeria, or Hutchinson-Gilford Progeria Syndrome (HGPS), is a rare and fatal genetic disorder in childhood, exhibiting features akin to premature aging. Despite normal appearances in infancy, affected children face accelerated aging with distinct facial characteristics, including micrognathia, dental malformations, lower body weight, early hair loss, decreased joint mobility, lipodystrophy, etc. The cause of HGPS is a point mutation that occurs at the exon 11 of the LMNA gene which normally produces Lamin A protein. This mutation leads to the formation of a mutated Lamin A protein known as progerin. Unlike normal Lamin A, progerin undergoes incomplete processing and remains permanently farnesylated and carboxymethylated. The persistent farnesylation of progerin disrupts the normal nuclear architecture and function. This abnormality contributes to various cellular defects observed in individuals with HGPS. Different therapeutic strategies are used to target progerin for the treatment of HGPS such as methylation and farnesylation inhibitors, gene therapy, development of biologicals, and a new age CRSIP-CAS9 but none of them can cure it. Despite the considerable work remaining, the progress in understanding progeria holds promise for the development of innovative treatment approaches. This study delves into the mechanism of progerin formation, changes in the body due to progerin, its complications, current therapeutic strategies, and recent advancements.

Keywords: Hutchinson-Gilford Progeria Syndrome (HGPS), Micrognathia, farnesylation, LMNA gene mutation, progerin, Methylation inhibitors and Gene therapy

INTRODUCTION

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Death and aging are inevitable parts of an organism's life cycle. Over the ages, there has been much discussion and investigation into the causes of aging and the mechanisms that underlie it. Within the past era, various researches have been done to understand the cause and physiological processes that lead to aging. Numerous studies have been conducted thus far on the aging process that conclude that some of the causes of natural aging are nuclear DNA damage which is linked with telomere shortening and leads to cell death, loss of epigenetic structure, increased DNA methylation, altered post-translational modifications, damage by ROS which oxidizes lipids, proteins and DNA and cause mutation [1, 2]. These alterations lead to the malfunction of cellular organelles, especially the mitochondria, which degenerates cells and tissues. Based on Hayflick's projections, the mitigation of

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primary mortality factors in senescence such as cardiovascular ailments, cerebrovascular incidents, and malignancies would yield a marginal enhancement in life expectancy, approximating an additional 15 years. This suggests that prolonging life doesn't mean achieving immortality; it merely extends our lifespan while we still undergo the aging process and eventually face mortality, albeit without specific age-related diseases [3]

Numerous scholars have observed similarities between the aging process and the hereditary condition known as Hutchinson-Gilford progeria syndrome (HGPS). An intermediate filament protein called lamin A, which is essential for preserving nuclear architecture, has been found to be mutated in HGPS [4]. Progerin is an abnormal form of lamin A caused by this mutation [5]. The mutation in question is specifically an in-frame deletion of 50 amino acids near the C- terminus of prelamin A, which is the precursor to mature lamin A. This is the consequence of a de novo single-base alteration in exon 11 of the LMNA gene (c.1824C>T), which triggers a cryptic splicing site [5]. By interfering with the location and quantity of chromatin remodelling factors, transcription factors, DNA repair factors, and factors related to the nuclear lamina, progerin results in cell death and dysfunction of the tissues and organs. It also decreases the level of antioxidant proteins which will become the cause of change in nuclear and chromosomal structure [2].

Why Do We Age?

Prominent theories in the field of aging, such as the free radical theory [6], the immunologic theory [7], the inflammation theory [8], and the mitochondrial theory [9], identify particular factors as central contributors to the aging process. By focusing on these factors, each theory provides valuable and nuanced perspectives on the physiological changes that occur as individuals age, enriching our comprehension of the aging phenomenon.

According to the evolutionary theory of ageing, ageing happens as natural selection's force wanes. This concept was established in the 1940s through observations of Huntington’s disease patients. Despite the potentially strong selection against this dominant lethal mutation, the disease persisted in the population [10]. This persistence can be attributed to the late onset of symptoms (around 30–40 years), allowing carriers to reproduce before succumbing to the disease. The evolutionary theory of aging and Darwin's theory of natural selection both suggest that organisms modify their lifespans in response to environmental stresses [11,12]. Evidence from animals in protected environments, like zoos, supports this idea by showing longer lifespans. For example, research comparing mainland and island opossums revealed that protected island populations live longer, confirming the theory's predictions. However, the "disposable soma theory of aging" suggests that investing in longevity may reduce resources available for reproduction, influencing lifespan. Experiments in fruit flies and nematodes have shown that limiting reproduction can extend lifespan, emphasizing the trade-off between reproduction and longevity [13].

In the 1950s, Harman proposed the free radical theory of aging for the first time. He postulated that aging and eventual death are universal processes that affect both inherited and environmental factors in organisms. In 1972, Harman revised the theory, identifying mitochondria as the primary source of most free radical reactions associated with aging. Moreover, it has been postulated that the lifespan of an organism is impacted by the pace at which free radicals inflict damage upon mitochondria [14,15]. The free radical theory of aging postulates that mutations in mitochondrial DNA might hasten oxidative damage by upsetting the electron transport chain, which increases the discharge of free radicals and causes further mutations in the mitochondrial DNA. Cellular malfunction and aging may eventually result from this cycle of mutation and oxidative stress [16]. In addition, an additional aspect of the hypothesis contends that as organisms age, their ability to degrade proteins is reduced, which leads to an accumulation of oxidized proteins within cells, impairing cellular function and hastening the aging process [17].

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The idea of mitochondrial aging postulates that malfunctions in metabolic pathways are the cause of age-related deterioration. Mitochondrial DNA (mtDNA), though a small fraction of total genetic material, significantly impacts cellular physiology. Since mitochondrial DNA (mtDNA) lacks protective histones and is located close to locations where oxygen radicals are generated, oxidative damage can occur. Oxidized base levels, which are thought to be 10 to 20 X higher than those seen in nuclear DNA, are indicative of this vulnerability. Mutations in mtDNA disrupt the electron transfer chain, crucial for cellular energy production, affecting cellular energetics and contributing to aging [18, 19]. These mutations can alter assembly and function of electron transfer chain components, with broad implications for cellular function.

Thus, despite its size, mtDNA's role in cellular physiology is substantial, and its integrity crucial for maintaining cellular health and functionality [20].

The telomere theory of aging, proposed in 1965, suggests that cellular aging occurs due to a finite limit in cell divisions [21], linked to the shortening of telomeres, specific DNA sequences at chromosome ends. Telomeres, consisting of repeated TTAGGG sequences [22], are maintained by telomerase, a ribonucleoprotein reverse transcriptase enzyme [23]. In order to maintain the stability of chromosome termini and prevent them from being recognized as double-stranded breaks, which may result in DNA damage, telomerase activity works to prevent telomere shortening. However, the gradual decline in telomerase activity results in telomere attrition. This attrition can cause chromosomal abnormalities such as translocation, fusion, or rearrangement, ultimately contributing to cellular aging and senescence [24]. Therefore, the synthesis of telomeres by telomerase plays a critical role in maintaining chromosome integrity and preventing age-related cellular dysfunction.

Causes of Aging

Aging, an intricate biological process, reflects the culmination of numerous factors spanning genetic predispositions to environmental impacts. While aging is an inherent aspect of life's journey, its intricate causes have long intrigued scientists. Through exhaustive research, various theories have been posited to unveil the intricate mechanisms driving aging. From oxidative stress and DNA damage to cellular senescence and mitochondrial dysfunction, each theory offers unique insights into this complex phenomenon. Understanding the multifaceted interplay of these factors is paramount for unraveling the mysteries of human biology and devising strategies to foster healthy aging.

Oxidative Damage

There is a widely held belief that aging and metabolism are related, and that this relationship exists regardless of genetic changes. Aging is closely related to an organism's regular metabolic functioning. A portion of oxygen molecules in mitochondria are not fully processed during metabolism, which leads to the production of ROS including hydrogen peroxide, superoxide ions, and hydroxyl radicals. These ROS have the power to oxidatively destroy proteins, nucleic acids, and membranes within cells. The notion is corroborated by research employing Drosophila melanogaster. Research suggests that overexpressing ROS-degrading enzymes such as catalase and superoxide dismutase increases. Drosophila longevity by about 30–40% as compared to control populations [25,26]. Additionally, research has shown that Drosophila harboring mutations in the methuselah gene—named for the long-living biblical character—have a about 35% longer lifetime than wild-type flies. These genetically modified flies exhibit increased resistance to paraquat, a toxin known to cause the production of reactive oxygen species (ROS) in cellular settings. These results demonstrate both the importance of inherited variables in the regulation of aging processes and support the concept that ROS play a major role in the aging phenomena [27]

Mechanism

Oxidative damage is brought on by ROS, which are created mostly in mitochondria during cellular metabolism. ROS are produced when partial oxygen reduction occurs in the electron transport cycle.

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Peroxisomes and cytoplasmic enzymes are further sources. By initiating cascade reactions, these ROS harm DNA, lipids, and proteins [28]. Cells employ many antioxidant defense mechanisms to combat the effects of ROS. These mechanisms include enzymes like catalase and superoxide dismutase as well as non-enzymatic antioxidants like glutathione and vitamins C and E. Cellular damage results from a disruption of the ROS-antioxidant equilibrium, which accelerates aging and illness. Cellular homeostasis and general health depends on maintaining this balance [29].

Telomerase Shortening

Shortening of telomere has been proposed as a putative mechanism underlying cellular senescence, with initial observations indicating a finite replicative capacity of cells in vitro due to progressive telomere attrition [30]. The introduction of telomerase, capable of preserving telomere length, has supported the concept of telomeres acting as a "clock" regulating cellular replicative potential. Nevertheless, subsequent investigations have challenged this oversimplified perspective. Studies have failed to establish a direct correlation between telomere length and organismal lifespan, with significant interspecies variations noted. Additionally, the relationship between telomere length and chronological age in humans appears complex and multifaceted [31, 32].

Insights gleaned from experiments utilizing telomerase-deficient mice have further nuanced our understanding. Contrary to expectations, these mice did not manifest significant aging phenotypes, implying that telomere shortening may not be the primary determinant of aging kinetics [33, 34]. Rather, it is suggested that telomere-dependent inhibition of cell division might primarily function as a safeguard against carcinogenesis rather than solely serving as an "aging clock."

Mitochondrial Dysfunction and Somatic Mitochondrial DNA Mutations

A state where mitochondria, the cell's energy factories, experience impaired function. This impairment results in decreased energy production, heightened oxidative stress, and disruptions in cellular processes. Somatic mitochondrial DNA (mtDNA) mutations are alterations in the mitochondrial genome that occur within individual cells during an organism's lifetime [35]. These mutations primarily arise from spontaneous errors during mtDNA replication or damage repair processes. The most common types of somatic mtDNA mutations are point mutations and deletions. These mutations may accumulate due to a range of factors, encompassing replication errors and exposure to oxidative stress. These mutations play a role in the aging process, thereby contributing to a deterioration in cellular function and tissue integrity [36,37]. The accumulation of mtDNA mutations with age is well-documented and is associated with mitochondrial dysfunction, contributing to the aging process. Various studies have shown an increase in the frequency of mtDNA mutations, including point mutations and deletions, in tissues such as the brain, heart, skeletal muscles, and liver as individuals age [38,39,40]. In particular, mtDNA deletion mutations have been observed to accumulate intracellularly, leading to segmental electron transport chain (ETC) abnormalities, tissue atrophy, oxidative damage, and conditions like sarcopenia (muscle loss) [41,42]. Additionally, specific mtDNA deletions, such as the 4977 bp deletion (common deletion), have been found to increase with age in different regions of the human brain[43]. Studies have shown that even a small proportion of neurons with respiratory chain deficiency (less than 20%) in the forebrain of chimeric mice can lead to neuronal mitochondrial dysfunction and neurological disease. Additionally, research on normal aging brains has revealed an increase in the number of neurons with cytochrome c oxidase (COX) deficiency in regions like the substantia nigra and hippocampus. This finding indicates that defects in complex IV of the electron transport chain significantly rise with age, contributing to mitochondrial dysfunction. Essentially, even a minor impairment in mitochondrial function within specific brain regions can have profound effects on neuronal health and may contribute to age-related neurological disorders [44].

The multifaceted impact of somatic mtDNA mutations on aging and age-related diseases is profound.

- *Functional Repercussions:* Somatic mtDNA mutations affect the mitochondria's capacity to function normally, which affects essential biological processes like energy production, signaling

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pathways, and metabolism.Studies reveal that mtDNA mutations-induced mitochondrial dysfunction plays a major part in the age-linked decline in tissue integrity and health[45].

- *Oxidative Stress:* A mutation in the mtDNA might cause an rise in the mitochondria's production of ROS. These reactive oxygen species (ROS) speed up age-related cellular deterioration and exacerbate mitochondrial dysfunction by oxidatively damaging cellular components. Therefore, oxidative stress is made worse by somatic mtDNA mutations, which accelerates aging [46].
- *Muscle Aging and Sarcopenia:* Somatic mtDNA mutations in skeletal muscle cells are associated with sarcopenia, the age-related loss of muscle mass and strength. Mitochondrial dysfunction in muscle cells leads to impaired muscle function, decreased mobility, and reduced quality of life in older individuals.

PROGERIN AND NATURAL AGING

To investigate progerin expression in unaffected individuals, 150 skin biopsies were collected from healthy neonates of both genders. RT-PCR screening targeting exons 9 and 12 revealed a low level of progerin mRNA, which showed no association with age. However, sequencing of cDNA from a 97-year-old individual matched the progerin sequence. Monoclonal antibody screening detected minimal progerin in samples from older individuals only, suggesting an age- related increase in progerin incidence [47]. Immunofluorescence microscopy using anti-progerin antibodies on fibroblast cells at different population doublings showed a rise in progerin- positive cells from early to late doublings, especially evident in cells from HGPS patients. Cultures from young subjects exhibited minimal progerin-positive staining, while those from elderly subjects showed a slight increase. These progerin-positive cells displayed nuclear abnormalities akin to HGPS fibroblasts, indicating abnormal cell cycle behavior. Additionally, normal fibroblast cultures showed a gradual increase in progerin-positive cells with cellular aging, suggesting age-dependent accumulation of progerin in these cultures.

To examine progerin's cellular distribution, immunohistochemistry was conducted on slices obtained from skin biopsies and neonatal foreskins from individuals aged 22 to 93 years [47]. Newborn foreskin showed no progerin signal. However, in adult skin sections, progerin- positive cells were observed in varying numbers in different layers of the dermis, with a notable increase in older individuals, suggesting age-related progerin accumulation. Progerin-positive keratinocytes were localized mainly in the upper layers of the epidermis, with sporadic distribution. Elderly skin sections exhibited higher levels of progerin-positive keratinocytes, concentrated near the skin surface 47. In skeletal muscle cells from individuals aged 16 to 71 years, elevated progerin transcript levels were associated with increased transcription rather than splicing errors. Progerin protein levels varied significantly but showed no correlation with age [48,49].

In fibroblast cultures from individuals aged 81 to 96 years, nuclear abnormalities and reduced levels of HP1 and Tri-Me-K9H3 were observed, similar to HGPS cells [50]. There were more nuclear flaws in both young and old cell lines, with the accumulation occurring more quickly in the older cell lines. Elevated nuclei with phosphorylated histone H2AX foci, indicative of unrepaired DNA damage, were observed in cells from older individuals compared to younger ones. The presence of Δ50 lamin A, due to aberrant splicing of LMNA mRNA, contributed to nuclear defects, which were reversible with morpholino oligonucleotide treatment targeting the cryptic splice site of exon 11. Suppression of this splicing junction correspondingly attenuated indicators of cellular senescence and augmented cellular proliferation [50].

Formation of Progerin

A complex network of Lamin proteins from the intermediate filament type V family makes up the nuclear lamina. LMNA, LMNB1, and LMNB2 are three different forms of these lamins. There are four A-type lamin isoforms (A, C, CΔ10, and C2) resulting from alternative splicing of the LMNA gene, which has twelve exons. Lamins protect genetic material and form links between the cytoskeleton and

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the nuclear skeleton. They are important components of nuclear structural organization, size, and placement. When lamin A is first produced in the cytosol, it is a 664-residue prelamin A [51,52,53]. However, after post-translational modifications, such as the removal of 18 amino acids, lamin A matures into a 646-residue version. It takes around three hours to complete this post-translational alteration of prelamin A [54]. At its carboxyl terminus, prelamin A has a CaaX box and two endoproteolytic sites. Farnesyltransferase catalyzes the farnesylation of the cysteine residue at the CaaX motif, while RAS converting enzyme 1 catalyzes the proteolytic cleavage of the other three amino acids (Fig 1). The esterification of the farnesylated cysteine with a methyl group at the C-terminus during post-translational modification is then mediated by isoprenylcysteine carboxyl methyltransferase (ICMT). Zinc ion-dependent metalloprotease ZMPSTE24 helps convert farnesylated prelamin A to mature lamin A by cleaving off 15 amino acids from the carboxyl terminus. This produces mature lamin A [54]

In case of Progerin there is de novo single base substitution within exon 11 at nucleotide 1824 in which cytosine is replaced by thymine [5]. However, this mutation does not have any effect on the translated amino acid but it was found that it affects the post translational modification of the protein (prelamin A). This mutation causes removal of 50 amino acids near the c terminus of exon 11 [55]. It leads to the loss of second site of endoproteolytic cleavage which is necessary for the removal of 18 amino acids from the c terminus for the formation of mature lamin A and cause permanent farnesylation and carboxymethylation of prelamin A (Figure 1). The mutated protein is known as ‘Progerin’. Progerin then interferes with the functions performed by Mature Lamin A and causes nuclear abnormalities, telomere shortening, cellular decline, misregulated gene expression and all of them together leads to premature aging.

Molecular Changes Due to Progerin

Progerin is a lamin A protein variation that causes telomere attrition more quickly, which in turn causes DNA strand breaks and the loss of telomeric capping proteins [56,57]. Consequently, this cascade culminates in cell cycle arrest and cellular senescence. This phenomenon is corroborated by elevated β-galactosidase activity linked with senescence in afflicted fibroblast cells [57]. Moreover, decreased telomere integrity seems to worsen progerin production, suggesting a feedback loop. HGP patients' fibroblast cells show reduced telomerase immortalization, indicating a resistance to telomere maintenance [58-60]. Partially mediating the progerin-telomere interaction that leads to cellular senescence is p53 activation. This interaction is a pivotal determinant in cellular aging, alongside dysregulated gene splicing [61-63].

Progerin also inhibits nuclear factor erythroid 2-related factor 2 (NRF2) production and prevents it from binding to sequences known as antioxidant response elements (AREs), which promotes the build-up of ROS and hinders the body's antioxidant defense system [63, 64] . Increased ROS levels cause DNA double-strand breaks (DSBs) to worsen and prevent fibroblast growth. Progerin increases the generation of ROS, which delays the repair of DNA damage caused by ROS and prolongs cellular senescence [64]. Through stress-activated protein kinase pathways, ROS can potentially cause apoptosis. Increased reactive oxygen species (ROS) accelerate telomere deterioration and single-stranded telomeric DNA damages, which in turn trigger senescence [65,66].Subsequent to telomere attrition, p53 triggers cell cycle arrest by inhibiting peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and PGC-1 beta, critical regulators of mitochondrial function [67,68].Thoroughly understanding how progerin affects telomeres and oxidative stress offers important new understandings of the pathophysiology of illnesses associated with accelerated aging, and maybe opens up new treatment paths [69].

Analysis of gene expression patterns in HGPS fibroblast cell lines revealed dysregulation in 361 genes, with 193 exhibiting upregulation and 168 showing downregulation Notably, a substantial proportion of these dysregulated genes encode transcription factors primarily associated with the control of tissue differentiation and embryonic development [70-72].

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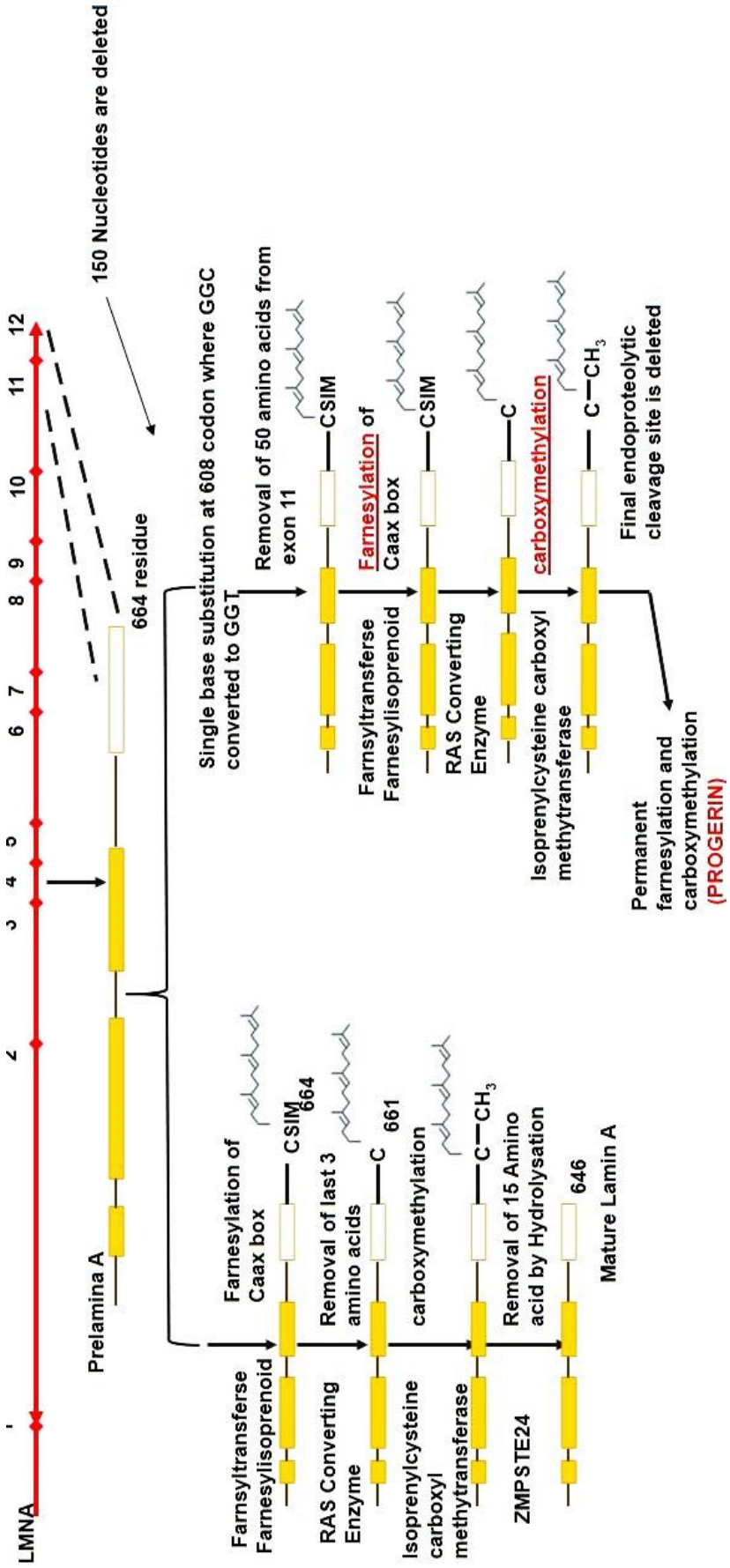

Figure 1. Formation of Progerin.

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The significantly elevated gene MEOX2/GAX controls the growth of mesodermal tissue. Affected genes also included type IV collagenase and netrin4, which influence cardiomyocytes, cardiovascular endothelium, bone, cartilage, and adipose tissues [73-75]. These 30 genes are linked to the creation of an extracellular matrix (ECM). Reduced nuclear lamina binding to pericentric areas, which is linked to HP1 protein loss, modifies chromatin architecture by downregulating H3K9me3 and H3K27me3 heterochromatins [76,77]. Chromatin structure is impacted by decreased H3K9me3 levels, which hinder nuclear lamina-pericentric region association. Chromatin flexibility is disrupted by progerin's weak interaction with LAP2α, which is caused by decreased expression of LAP2α and H3K9me3. Furthermore, progerin modifies BAF localization, which is essential for lamin A/C activities, chromatin and nuclear lamina integrity [78-80]. The function of progerin in natural aging is highlighted by these chromatin organization alterations, which are similar to those observed in aged cells. This work defines the chromatin changes linked to aging and clarifies the complex molecular pathways involved in the HGPS pathogenesis.

The link between transcription factors and signaling molecules is facilitated by Lamin A, which acts as a platform for signaling [81-83]. Dysregulated differentiation processes arise from progerin production, which interferes with important signaling pathways like Wnt and Notch. Additionally, dilated cardiomyopathy and stress responses are triggered by mutant lamin A's hyperactivation of the ERK1/2, JNK, AKT, and p38α signaling [79]. Additionally, progerin modifies the way that lamin A interacts with vitamin D receptors, affecting nuclear localization and probably causing aging symptoms that are similar to those of HGPS. Low leptin expression and tiny adipocytes are signs of vitamin D receptor insufficiency, which is similar to HGPS and impacts oxidative phosphorylation and adipogenesis [84,85]. Progerin-positive cells' overactive NF-κB signaling suggests that it plays a part in early aging. Nuclear morphological abnormalities are observed in HGPS, including progerin-induced changes in nuclear architecture-related genes like BAFs [86,87]. Nuclear envelope reassembly and chromosomal segregation are hampered by these modifications. In HGPS fibroblasts, methylation abnormalities impact epigenetic regulation and signaling pathways, representing both spontaneous and accelerated aging processes [88-91]. Comprehending these molecular modifications offers valuable understanding of the etiology of HGPS and aging-related abnormalities [92-95]

HOW CAN WE TARGET PROGERIN?

Figure 2 The pathological cornerstone of HGPS resides in the aberrant accumulation of progerin, a truncated and toxic form of the nuclear envelope protein lamin A. In the pursuit of effective therapeutic interventions, considerable attention has been directed towards developing strategies that specifically target progerin's production or post-translational modification, particularly its isoprenylation [96].

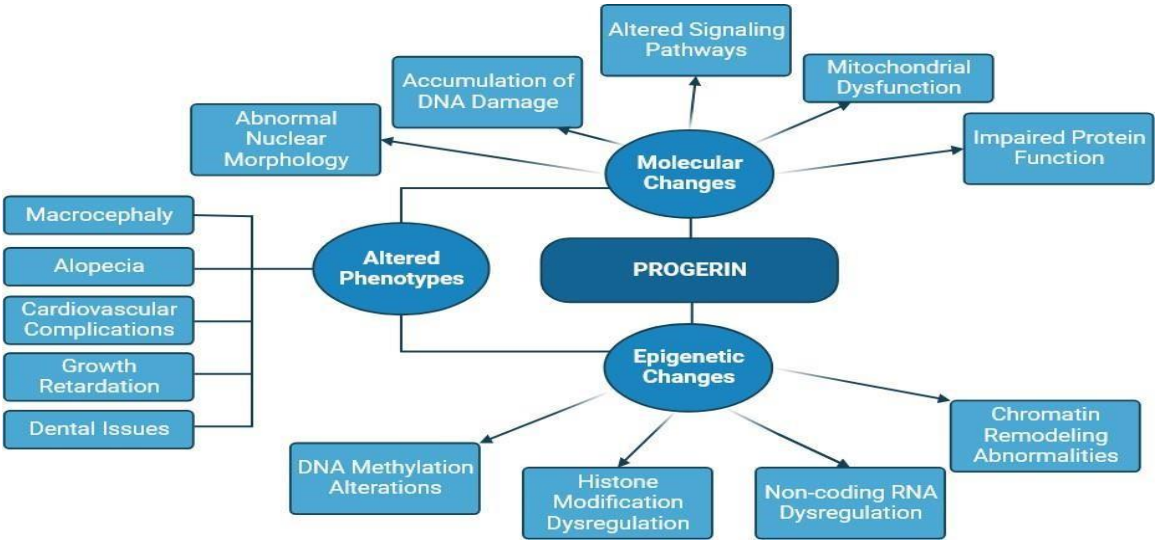

Figure 2. Epigenetic and morphological changes due to progerin formation.

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Such approaches represent a multifaceted endeavor to attenuate the deleterious consequences associated with progerin's presence, aiming to mitigate the myriad pathological manifestations observed in individuals afflicted with HGPS. This concerted effort underscores the intricate interplay between molecular mechanisms and clinical outcomes, illuminating potential avenues for therapeutic innovation and the amelioration of HGPS-related morbidity and mortality.

Correction of LMNA Mutation through Genome Editing

The exceptional specificity of gene editing techniques makes them highly promising for correcting the underlying mutation causing HGPS [97]. Among the most useful tools in this regard, however, are adenine base editors (ABEs). By precisely transforming selected A•T base pairs into G•C base pairs, adenine base editors (ABEs) eliminate the need for donor DNA templates or double-stranded DNA breaks and enable mutation repair [98] . Positive results have been obtained with this method, since HGPS-derived fibroblasts and mouse models have successfully restored normal LMNA transcript splicing. Thus, treated fibroblasts showed decreased progerin levels and improved nuclear morphological abnormalities, whereas HGPS mice treated with ABE showed improved splicing, decreased progerin expression, rescued vascular diseases, and longer lifespans. Additionally, the CRISPR/Cas system has shown promise in correcting mutations in HGPS murine fibroblasts, leading to significant improvements in aberrant nuclear morphologies and notable decreases in progerin-positive nuclei [99,100]. When HGPS mice were given systemic infusion of CRISPR-Cas9 components provided by an adeno-associated virus, their levels of lamin A/progerin reduced, and their physiological parameters improved and their lifespans increased. Although these developments highlight the potential of gene-editing methods in HGPS therapy, it is critical to address related drawbacks, such as chromosomal off-target effects and possible adverse effects associated with viral delivery systems, prior to clinical translation [101].

Modulation of Mis-splicing

Gilford-Hutchinson Mis-splicing events within LMNA gene exon 11 are the source of Progeria

Syndrome (HGPS). Progerin expression can be decreased with antisense oligonucleotides (ASOs) by favoring the synthesis of lamin C over progerin. Progerin levels in patient-derived fibroblasts and mouse models have been successfully reduced by targeting ASOs to exon 11 of the LMNA gene. Targeting the LMNA intron 11/exon 12 junction, 198 ASOs have been screened recently. An optimized ASO that can decrease progerin mRNA and protein expression and prolong longevity in HGPS animal models was found [102,103].Furthermore, progerin mRNA levels in patient-derived fibroblasts and murine aortas have been demonstrated to be effectively decreased by antisense peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs), such as SRP-2001.Moreover, antisense peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs), such as SRP-2001, have demonstrated effectiveness in reducing progerin mRNA levels in murine aortas and patient-derived fibroblasts, saving vascular smooth muscle cell loss, and extending life span in HGPS animals [104]. However, due to similarity between the alternative splice sites, ASOs' influence on lamin A and lamin C's alternative splicing patterns limits their potential for therapeutic use. Their clinical application must take this into serious consideration [105].

Progerin Clearance

The possibility of HGPS lies in accelerating the breakdown of progerin via the autophagy- lysosomal pathway. Rapamycin treatment in patient-derived fibroblasts enhances nuclear morphology and postpones the aging process by accelerating progerin turnover [106]. Additionally, it prolongs the lifetime of mice defective in lamin A/C by restoring cardiac and skeletal muscle function. HGPS patients are undergoing clinical trials with rapamycin derivatives such as Everolimus in conjunction with Lonafarnib. Furthermore, in HGPS-induced pluripotent stem cells and primary fibroblasts, the proteasome inhibitor MG132 stimulates the autophagic clearance of progerin, improving cell proliferation and lowering senescence. But continued use might have a wider impact on protein turnover.

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Additionally, Progerinin/SLC- D011 activates autophagy to break the connection between lamin A and progerin, which in turn causes progerin clearance. This varied strategy highlights the possibility of autophagy modulation for HGPS therapy, requiring additional study for clinical application confirmation [107].

Inhibition of Progerin Farnesylation

In HGPS, progerin, a faulty type of lamin A, mostly causes damage by farnesylation. The goal of early treatment strategies was to interfere with progerin farnesylation by using farnesyltransferase inhibitors (FTIs) [108]. FTI therapy had a modest effect on mitochondrial function, DNA damage, and cellular senescence in human HGPS fibroblasts, although it did improve nuclear morphology [109]. Administration of FTI improved cardiovascular and bone conditions in HGPS mice models, increasing longevity [110, 111].FTI Lonafarnib clinical trials in HGPS patients demonstrated moderate increases in life expectancy but also modest improvements in body weight, bone density, and cardiovascular health [112, 113]. Progerin, however, has the ability to use different prenylation routes, which lessens the efficacy of FTI. Progeroid animal models and HGPS fibroblasts demonstrated potential for combination therapy that target both geranylgeranylation and farnesylation, such as zoledronate and pravastatin, with some improvement in bone health [114].

Restoration of Mitochondrial Function

Numerous pharmaceutical therapies have been investigated to address mitochondrial dysfunction in HGPS. Treatment with the ATM inhibitor KU-60019 ameliorated cellular senescence in HGPS fibroblasts by enhancing mitochondrial membrane potential and reducing ROS generation. Methylene blue, an antioxidant, was linked to increased PGC-1α expression and decreased ROS levels while improving cellular shape, motility, and mitochondrial membrane potential [115]. In a similar vein, Y-27632, an inhibitor of ROCK1, promoted oxidative phosphorylation over glycolysis to reinstate mitochondrial respiration and lower ROS levels. Mitigate ROS accumulation by improving mitochondrial shape, membrane potential, and ATP levels through CRM1 inhibition with LMB. The Nrf2 activator sulforaphane improved membrane potential, ATP levels, and the generation of less reactive oxygen species (ROS) in progerin-expressing cells via restoring mitochondrial function. These methods show that treating mitochondrial dysfunction in HGPS may have therapeutic possibilities. Numerous pharmaceutical therapies have been investigated to address mitochondrial dysfunction in HGPS. By improving mitochondrial membrane potential and reducing ROS generation in HGPS fibroblasts, treatment with the ATM inhibitor KU-60019 helped to mitigate cellular senescence [115]. Methylene blue, an antioxidant, was linked to increased PGC-1α expression and decreased ROS levels while improving cellular shape, motility, and mitochondrial membrane potential. In a similar vein, Y-27632, an inhibitor of ROCK1, promoted oxidative phosphorylation over glycolysis to reinstate mitochondrial respiration and lower ROS levels [116]. ROS accumulation is reduced when CRM1 is inhibited with LMB, which also improves mitochondrial shape, membrane potential, and ATP levels. Additionally, the Nrf2 activator sulforaphane restores mitochondrial function in progerin-expressing cells, leading to better membrane potential, ATP levels, and reduced ROS generation [117]. These methods show that treating mitochondrial dysfunction in HGPS may have therapeutic possibilities [118-127].

CONCLUSION

A multifaceted interplay of oxidative damage, telomere shortening, and mitochondrial dysfunction drives aging. Understanding these mechanisms is crucial for developing strategies to promote healthy aging and mitigate age-related diseases, ultimately enhancing lifespan and quality of life. Investigating progerin expression in healthy individuals has revealed significant insights into the age-related increase of progerin and its impact on cellular function. Screening of skin biopsies and fibroblast cultures from individuals of various ages showed that progerin accumulates with cellular and organismal aging, resulting in nuclear abnormalities and cell cycle dysregulation akin to those seen in Hutchinson- Gilford Progeria Syndrome (HGPS). This phenomenon highlights the connection between progerin and natural aging processes. Targeting progerin for therapeutic intervention involves various strategies such as

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correcting the underlying LMNA mutation, enhancing progerin clearance, inhibiting its farnesylation, and restoring mitochondrial function. Gene editing techniques, particularly CRISPR/Cas9 and adenine base editors (ABEs), show promise in correcting the LMNA mutation, thereby reducing progerin levels and improving cellular morphology. Antisense oligonucleotides (ASOs) and peptide-conjugated morpholino oligomers (PPMOs) effectively reduce progerin expression by modulating splicing patterns, offering the potential for therapeutic use despite the need to address off-target effects and splicing pattern similarities. Progerin clearance through autophagy-inducing agents like rapamycin and proteasome inhibitors has demonstrated efficacy in improving cellular function and extending lifespan in animal models. Inhibition of progerin farnesylation using farnesyltransferase inhibitors (FTIs) and combination therapies targeting alternative prenylation pathways have shown moderate success in clinical trials, highlighting the need for further optimization. Restoring mitochondrial function through various pharmacological agents has been explored to address the mitochondrial dysfunction associated with progerin accumulation. Antioxidants, ROCK1 inhibitors, CRM1 inhibitors, and Nrf2 activators have shown potential in reducing reactive oxygen species (ROS) levels, improving mitochondrial membrane potential, and enhancing cellular function. In summary, understanding the molecular mechanisms of progerin formation and its pathological effects provides a foundation for developing targeted therapies for HGPS and potentially mitigating age-related cellular decline. Continued research into gene editing, splicing modulation, autophagy enhancement, farnesylation inhibition, and mitochondrial restoration holds promise for improving clinical outcomes and extending healthy lifespan in individuals affected by progeria and related aging disorders.

Future Directions

These therapeutics alone or their correct combination can be proved as a great anti-aging molecule for targeting progerin to increase life span. Clinical trials and in vivo studies of these molecules in cell lines or human fibroblasts of healthy individuals should be done to check their efficacy and side effects.

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