A Wrinkle in Time: Premature Aging in HGPS and RD

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Summary

The aging process can be accelerated by numerous cellular and molecular variables. Progeroid syndromes are one such example. The phenotypes of Hutchinson-Gilford Progeria Syndrome (HGPS) and Restrictive Dermopathy (RD) are both caused by an irregular pathway of the processing of prelamin A to mature lamin A, an integral component of the nuclear lamina. In wild-type cells, prelamin A undergoes farnesylation followed by cleavage that is carried out by the enzyme Zmpste24. A 50 amino acid deletion in the LMNA gene found in HGPS patients eliminates the cleavage site in prelamin A, causing an accumulation of farnesylated prelamin A. The buildup of this protein, known as progerin/LA∆50, occurs at the nuclear rim. In RD, nonfarnesylated and farnesylated prelamin A build up due to a deficiency in the Zmpste24 cleaving enzyme. In both syndromes, however, the accumulation of the different forms of prelamin A causes nuclear shape abnormalities and leads to phenotypes resembling premature aging. Currently, there are no known cures for HGPS and RD. However, FTIs and gene therapy are being studied as possible treatments. With continued research, more can be learned about the normal aging process, which could be applied in understanding progeroid syndromes and developing alternative treatments.

Introduction

Aging is a normal physiological process that can be altered by various cellular and molecular factors. Progeroid syndromes include multiple diseases in which premature aging occurs. Hutchinson-Gilford progeria syndrome (HGPS) and Restrictive Dermopathy (RD) are two such examples (The Progeria Research Foundation, 2006).

Since the late nineteenth century when HGPS was first described, approximately 100 known cases have been reported worldwide (Ackerman, 2002; Hennekam, 2006; Monu et al., 1990; The Progeria Research Foundation, 2006). It is estimated that HGPS affects 1 in 4 million children, while the actual estimation is 1 in 8 million (Ackerman, 2002; Hennekam, 2006; Monu et al.., 1990).

Children with autosomal dominant HGPS appear normal at birth and are usually diagnosed around two years of age (Hennekam, 2006; Wisuthsarewong, 1999). Diagnostic characteristics include cessation of growth and excessive weight reduction due to loss of subcutaneous fat, as well as a noticeable degeneration of skin, muscle, and bone. On average, this degenerative disease results in death during early adolescence due to heart failure (Wisuthsarewong, 1999; Hennekam, 2006).

HGPS phenotypes are a consequence of misshapen nuclei that interrupt a number of vital cell processes. In 2003, it was discovered that a missense mutation in the LMNA gene causes a 50 amino acid deletion in the transcribed protein prelamin A (Goldman, et al., 2004). This mutant prelamin A is unrecognizable by Zmpste24, the enzyme involved in the final processing step of prelamin A to mature lamin A (Goldman, et al., 2004). This leads to the buildup of farnesylated prelamin A on the nuclear membrane and has deleterious effects on the cell (Goldman, et al., 2004).

In Restrictive Dermopathy (RD), a more severe and rare form of progeria, a similar alteration in the processing of prelamin A occurs, leading to abnormally shaped cell nuclei (Navarro et al., 2005). In HGPS, a mutation affects the protein prelamin A directly, whereas in RD, a mutation deletes Zmpste24, which is necessary for processing mature lamin A (Navarro et al., 2005). This neonatal skin disease is fatal because rupture of the placental membrane results in a premature birth during approximately the thirty-fourth week of pregnancy (Navarro et al., 2005; Wesche et al., 2001). However, if infants live to term, they often die within several days of birth. As of 2001, there had been 35 reported cases worldwide (Wesche et al., 2001).

Overall, symptoms of RD are similar to that of HGPS, but more severe. Symptoms characteristic of RD include impaired motor and voluntary movement, abnormal joint function, low-set malformed ears, a small lower jaw and pinched nose, widely spaced eyes, and a fixed open mouth in a characteristic “o” shape (Moulson et al., 2005; Navarro et al., 2005; Wesche et al., 2001).

Given the infrequency of progeroid diseases worldwide, little attention has been paid to these premature aging syndromes. However, due to the recent discovery of their molecular mutations and pathologies, HGPS and RD have received greater attention in the past few years. Having identified the steps associated in the production of mature lamin A, as well as its role within a cell in relation to the normal process of aging, research is focused on potential treatments for both phenotypic and genotypic effects of these diseases (Eriksson et al., 2003). Presently, therapies for progeroid syndromes simply treat their associated symptoms; however, promising treatments include gene therapy and modification of lamin A processing through the use of pharmaceuticals (Fong et al., 2006; Scaffidi & Mistelli, 2005). Therapeutic intervention of these progeroid syndromes is at the forefront of current biological studies, which will hopefully yield results within the next few years.

The Genetic Basis of Normal Aging

Before 2003, the molecular foundations of HGPS and RD were unknown (Badame, 1989; The Progeria Research Foundation, 2006). However, prior speculation focused on the possibility that a mutation in common aging genes, such as klotho, Methuselah, and sgs1, could potentially lead to genetic instability and accelerated aging.

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Klotho is one of several genes that affects the normal aging process when not expressed. The transcribed klotho protein is a hormone targeted primarily by the kidneys and cardiovascular organs, where it reduces insulin receptor substrate (IRS) protein activity, as well as insulin and IGF1 signaling (Kurosu et al., 2005). These processes have evolved due to their suppressive aging qualities (Kurosu et al., 2005). Kurosu et al. (2005) observed that all mouse models expressing the klotho hormone exhibited normal aging. However, in mice where the klotho gene was not expressed, symptoms associated with aging were observed, especially degeneration in aforementioned target organs (Takahashi, 2000). Aging symptoms related to the absence of klotho include atherosclerosis, osteoporosis, emphysema, and infertility (Arking et al.., 2002). When the klotho protein was reintroduced into these knockout mice, the aging phenotypes observed were significantly decreased, suggesting that klotho plays a critical role in controlling aging and organ degeneration (Takahashi, 2000).

Another anti-aging gene, Methuselah, is involved in stress response pathways and is associated with regulating longevity (Lin et al.., 1998). Lin et al. (1998) demonstrated that excessive expression of the Methuselah gene in fruit flies increased life-span by about 35% compared to wild-type flies (Lin et al.., 1998). These findings suggest that the Methuselah gene is critical for a cell's survival due to its ability to maintain homeostasis.

The sgs1 gene, a member of the helicase family, is involved in maintaining genomic stability, chromosome segregation during mitosis, and DNA replication (Sinclair et al.., 1997). Given its role in cell division and genetic organization, the absence of sgs1 contributes to accelerated aging (Sinclair et al., 1997). Sinclair et al. (1997) used a yeast model to compare normal aging in wild-type cells to accelerated aging in sgs1-deficient yeast. Yeast deficient in sgs1 had a 60% shorter life span than the wild-type yeast. Additionally, premature sterility was observed when sgs1 was absent (Sinclair et al.., 1997). Cell division is reduced when sgs1 is not expressed, slowly leading to tissue and organ deterioration and contributing to the aging process.

The genetic and phenotypic effects of abnormal functioning of klotho, Methuselah, and sgs1 are comparable to the premature aging seen in HGPS and RD. Further investigation of aging genes could lead to a better understanding of the aging process.

Cause for Premature Aging: Altered Nuclei

Although discoveries about the abovementioned genes provided insight into aging, they did not account for HGPS and RD. It was thus necessary to use an alternative approach to identify the molecular basis of these premature aging diseases. Given that HGPS and RD cells are characterized by misshapen nuclei, researchers turned to the structural aspects of the nucleus for answers (Eriksson et al, 2003).

Nuclear Lamins

Lamins are a class of intermediate filament proteins that polymerize in order to form the nuclear lamina, a two-dimensional mesh structure located on the surface of the inner nuclear membrane, as seen in Figure 1 (Alberts et al., 2004). The primary purpose of the nuclear lamina is to provide mechanical support for the nucleus, maintaining its shape and structural integrity (Cao et al., 2007). The lamins are also found throughout the nucleoplasm and are involved in a variety of functions, including DNA replication, transcription, chromatin organization, and apoptosis (Figure 1) (Goldman et al., 2004). Lamins are also significant in the process of assembling and disassembling the nucleus during cell division (Alberts et al., 2004).

Lamins are divided into two sub-categories, A-type lamins and B-type lamins, which differ according to their primary sequence, pattern of expression, and biochemical properties (Goldman et al., 2004). The LMNA gene encodes the A-type lamins: lamin A, lamin C, lamin C_2, and lamin AΔ10 (Cao et al., 2007). The gene contains twelve exons and encompasses approximately 25 kilobases of genomic DNA (Eriksson et al., 2003). Mutations in the LMNA gene have been implicated as the cause of a number of genetic disorders that are collectively classified as laminopathies (Eriksson et al., 2003).

Lamin A Synthesis: A Multi-Step Process

Lamin A synthesis occurs at the periphery of the nuclear envelope and includes a number of processing steps that change the precursor protein, prelamin A, into mature lamin A (Figure 2a). After translation of prelamin A from the LMNA gene, the CAAX motif at the carboxyl terminus undergoes farnesylation followed by the proteolytic cleavage of the AAX sequence and carboxymethylation (Goldman et al., 2004). Finally, the last fifteen amino acids on the C-terminus of prelamin A are cleaved by the endoprotease Zmpste24, producing the mature, unfarnesylated lamin A (Sinesky et al., 1994).

Mutations in lamin A have been observed, to a lesser degree, in the cells of healthy individuals as they age (Scaffidi & Misteli, 2006). This suggests that lamin A plays a role in normal physiological aging, thus implying that mutations disrupting lamin function could additionally play a role in accelerated aging diseases.

Hutchinson-Gilford Progeria Syndrome

Having identified the role of nuclear lamina in maintaining nuclear integrity and cellular processes, the link between misshapen nuclei seen in HGPS became clear in 2003 when a mutation in the LMNA gene was implicated as the cause of HGPS (Eriksson et al., 2003; The Progeria Research Foundation, 2006). A mutation found in the LMNA gene in HGPS patients leads to an alteration in the transcribed lamin A protein, resulting in the classification of HGPS as a laminopathy. Studies have shown that the mutated lamin A protein is responsible for alterations in the shape and structure of HGPS cell nuclei, as well as in disrupting the normal cell cycle and mitosis. Furthermore, these cellular abnormalities are thought to contribute to the characteristic phenotypes associated with HGPS.

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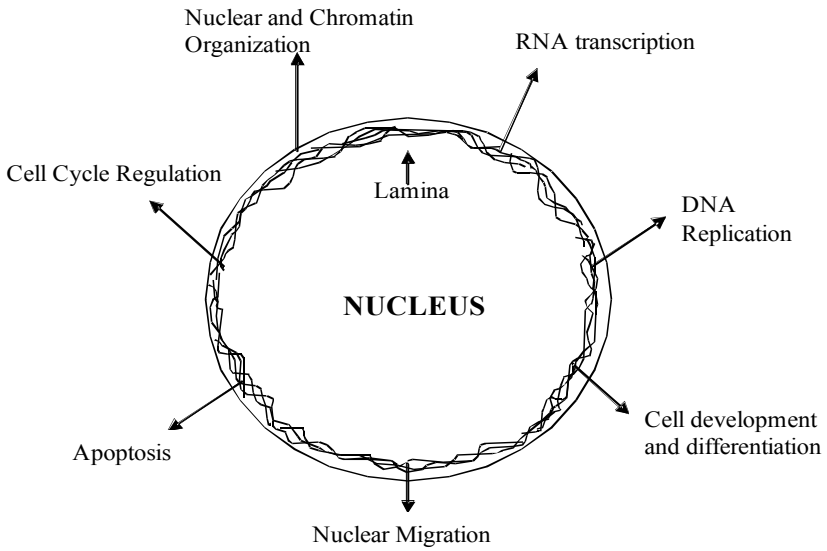

Figure 1. The Importance of the Nuclear Lamina. The nuclear lamina are intermediate filaments that create a meshwork of head to tail polymers lining the nucleoplasmic surface of inner nuclear membrane. Nuclear lamina provide structural support for the nucleus, allowing it to maintain its shape. Additionally, lamina aid in organizing nuclear processes such as, DNA replication, RNA transcription, interphase heterochromatin anchoring, mitosis, cell cycle regulation, and apoptosis. In the absence of nuclear lamina, not only is the integrity of the cell compromised, but many cellular processes are disrupted.

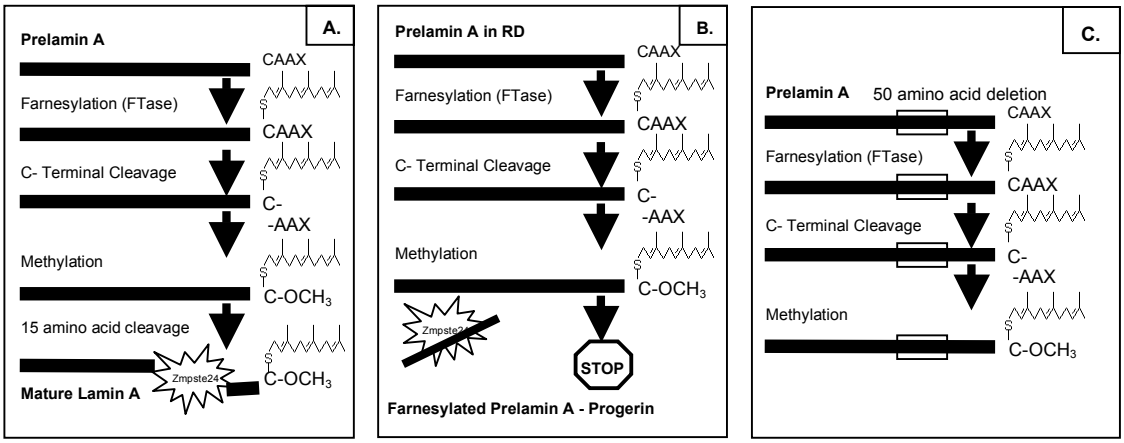

Figure 2. Pathways of Prelamin to Lamin A.
A: In a wild-type cell, farnesylation of a lipid anchor occurs, followed by cleavage and methylation at the C-terminus. The Zmpste24 enzyme then cleaves to form mature Lamin A.
B: The lack of Zmpste24 found in RD prevents the final cleavage needed to form mature lamin A.
C: The deletion in HGPS eliminates the cleavage site, resulting in a buildup of farnesylated prelamin A (progerin).

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Mutations in the LMNA Gene

Most cases of HGPS are associated with a *de novo,* or newly generated and not inherited, point mutation in exon 11 of the LMNA gene (Eriksson et al., 2003). This mutation involves a single-base substitution at position 1824 (GGC > GGT) but does not cause an amino acid change (Eriksson et al., 2003). Rather, the mutation results in the activation of a cryptic splice site, producing a mRNA molecule that lacks 150 nucleotides within exon 11. The resulting prelamin A molecule contains an internal deletion of 50 amino acids near the C terminus (Eriksson et al., 2003). This prelamin A undergoes farnesylation, but lacks the site for endoproteolytic cleavage by Zmpste24 and thus retains its farnesylated CAAX box motif. It is therefore incapable of forming mature lamin A (Figure 2c) (Eriksson et al., 2003). Furthermore, the deletion includes the elimination of at least one phosphorylation site for lamin A (Eriksson et al., 2003). The abnormal lamin A protein that is produced is referred to as progerin or LAΔ50. Production of lamin C is unaffected by the LMNA mutation.

Changes in Nuclear Architecture

The accumulation of progerin/LAΔ50 within cell nuclei can be associated with substantial changes in nuclear architecture. The protein progerin/LAΔ50 is targeted to the nuclear rim, where it disrupts the integrity of the nuclear lamina, producing severely misshapen nuclei (Eriksson et al, 2003). Moreover, when bacterially expressed progerin/LAΔ50 was injected into healthy fibroblast cells, many of the cell nuclei resembled HGPS cells, indicating that the mutant protein has a direct and immediate effect on nuclear shape (Goldman et al., 2004).

The architectural irregularities observed in HGPS cells include lobulation or blebbing of the nuclear envelope, as well as thickening of the nuclear lamina, loss of peripheral heterochromatin, and clustering of nuclear pores. Moreover, the expression of progerin/LAΔ50 leads to genome instability, DNA repair defects, and changes in histone methylation (Goldman et al., 2004; Dechat et al., 2007). The structural defects observed in cell nuclei worsen as the cells age, indicating that the increasing concentration of the mutant protein amplifies its deleterious effects on the cell (Goldman et al., 2004).

Cell Cycle Abnormalities

The presence of progerin/LAΔ50 has also been associated with disruptions in the progression of the cell cycle, including mitotic defects. During mitosis, progerin/LAΔ50 mislocalizes into insoluble cytoplasmic aggregates and membranes, causing abnormal chromosome segregation and binucleation (Cao et al., 2007). Furthermore, progerin/LAΔ50 interferes with the targeting of the components in the nuclear lamina into daughter cells during early G_1, delaying the onset and progression of cytokinesis (Dechat et al., 2007). This aggregation has also been associated with abnormalities in the retinoblastoma protein (Rb)-mediated transition from G_1 to S phase as a result of the inhibition of cdk4 activity (Dechat et al., 2007). Interestingly, studies have indicated that the abnormalities observed in nuclear architecture and in various stages of the cell cycle that are attributable to the expression of progerin/LAΔ50 in HGPS may also contribute to normal human aging (Cao et al., 2007; Dechat et al., 2007; Scaffidi & Misteli, 2006).

Restrictive Dermopathy

Following the identification of the genetic mutation causing HGPS, researchers began to investigate the cellular and molecular basis of a similar but more severe premature aging syndrome, Restrictive Dermopathy (RD). Subsequent studies have found mutations in the LMNA gene itself, as well as mutations in the gene for the Zmpste24 enzyme within the genomes of RD patients (Navarro et al., 2004). These mutations have been associated with an interruption of the processing pathway of prelamin A to lamin A in addition to the accumulation of truncated prelamin A in cell nuclei. Hence, RD has been classified as one of the most terminal laminopathies identified in humans to date (Navarro et al, 2004).

Genetic Mutations in RD

Studies have only isolated two types of genetic mutations thus far that can be associated with RD, including splicing mutations in the LMNA gene and an insertion within the ZMPSTE24 gene, also known as FACE-1 in humans (Navarro et al., 2004). The less common mutation, which affects the LMNA gene, is similar to that seen in individuals with HGPS. It involves the complete or partial deletion of exon 11 of the LMNA gene, which results in the production of truncated prelamin A that can not be modified to form mature lamin A (Navarro et al., 2004). It is likely that the mutations within the LMNA gene are coupled with one or more additional mutations, which would account for the greater severity of disease phenotypes in these individuals in comparison to HGPS patients with similar LMNA mutations (Narvarro et al., 2004).

In the majority of the individuals studied by Navarro et al. (2004), however, there was a mutation within the ZMPSTE24 gene, which codes for the endoprotease Zmpste24. This enzyme is known to be essential to the normal processing of prelamin A to mature lamin A. Furthermore, ZMPSTE24 mutations were identified in all individuals with RD that participated in a study by Navarro et al. (2005). Most of these individuals had a thymine insertion within exon 9 of the ZMPSTE24 gene, leading to the creation of a

premature termination codon within the gene (Navarro et al., 2005). Consequently, these individuals lacked both the Zmpste24 enzyme and mature lamin A. (Navarro et al., 2005). This suggests that either Zmpste24 was not being expressed or was degraded within the cell after translation and thus could not function in the processing pathway of prelamin A to mature lamin A (Navarro et al., 2005).

Notably, research has suggested that the single, heterozygous mutation in the ZMPSTE24 gene alone can not be responsible for the RD phenotype, namely, the complete loss of Zmpste24 (Navarro et al., 2005). This conclusion was reached based on evidence that only a complete loss of the Zmpste24 protein can cause RD (Navarro et al., 2005). This deficit would only be possible, however, with homozygous mutations or multiple heterozygous mutations within the ZMPSTE24 gene (Navarro et al., 2005). This is consistent with the identification of several individuals homozygous for the ZMPSTE24 mutation in exon 9, as well as the identification of additional mutations in the ZMPSTE24 gene in the remaining RD patients (Navarro et al., 2005). Similar to HGPS, the accumulation of farnesylated prelamin A causes abnormalities in cellular architecture.

Treating the Lamin A Mutations

Presently, there are no known cures for progeroid syndromes. However, clinical studies are currently being implemented to investigate possible treatments for both the phenotypic and genotypic effects. One potential treatment involves targeting the formation and amount of prelamin A synthesized by silencing the LMNA gene or by artificially correcting the point mutation through gene therapy (Fong et al., 2006). Another pathway involves altering the prelamin A processing steps in order to inhibit the farnesylation of prelamin A.

FTI Treatment

Perhaps one of the most promising treatments for HGPS and RD are farnesyl-transferase inhibitors (FTIs). FTIs were initially considered for treating cancer patients because they were observed to correct abnormal CAAX processing in Ras proteins, leading to a decrease in tumor genesis (Gelb et al., 2006). Given the similar CAAX modification and processing between Ras proteins and prelamin A, it seems plausible that FTIs could be used to treat HGPS and RD as well (Gelb et al., 2006).

FTI treatment prevents farnesylation of prelamin A, the first step in lamin A processing. Having never acquired the farnesyl lipid anchor, mutant prelamin A is not targeted to the nuclear membrane but rather remains in the nucleoplasm (Gelb et al., 2006).

Currently, it has been supported that the short term effects of FTI treatment improve cell morphology. With the FTI treatment of fibroblast cells expressing the missense mutation associated with HGPS, there was an overall visual improvement of nuclear integrity along with a decrease in nuclear blebbing (Toth et al., 2005). Improvements in nuclear integrity were seen in correlation with a reduction in the buildup of progerin/LAΔ50 on the nuclear rim of FTI-treated HGPS cells (Toth et al., 2005). Additionally, nuclear shape abnormalities and the disrupted heterochromatin organization observed in HGPS cells can be recovered by treatment with a chromatin-modifying drug along with FTI treatment (Columbaro et al., 2005). In reorganizing nuclear components, as well as lowering progerin/LAΔ50 levels, improvement of nuclear morphology is dually accelerated.

Given the reduction of abnormal cell nuclei, the disease phenotypes common in HGPS also diminished with FTI treatment (Yang et al., 2006). Specifically, a decrease in weight loss, bone abnormalities, and loss of adipose tissue were observed in mice with a HGPS-like mutation (Yang et al., 2006). Reversing such phenotypes would ultimately result in a longer life span and greater survival rate, thus providing support for the use of FTIs as a potential therapy for HGPS.

Toth et al. (2005) treated fibroblasts from human RD patients with FTIs, and found that prelamin A was concentrated in the nucleoplasm, while untreated cells showed massive accumulation around the nuclear rim. FTI treatment of fibroblasts also reduced the percent of cells with misshapen nuclei. To further explore of the effects of FTIs on RD, Toth et al. (2005) examined Zmpste24-deficient cells using Zmpste24$^{-/-}$ mouse embryonic fibroblasts (MEFs) that had the Zmpste24 gene knocked out. Similar results found that two different FTIs clearly reduced the amount of prelamin A in the Zmpste24$^{-/-}$ MEFs.

Currently, there is adequate support for the treatment of HGPS and RD with FTIs. However, it is essential to obtain results from studies looking at the long-term effects of FTI treatment and to begin clinical trials in order to determine whether FTIs are safe and effective for use in humans as well.

Gene Therapy

Gene therapy is currently under investigation as an alternative treatment for HGPS and RD. One approach to this therapy involves inhibiting the expression of prelamin A. In 2006, Fong et al. revealed that lamin A appeared to be dispensable in mice cells, because the lamin C-only (Lmna$^{LCO/LCO}$) mice they created were completely healthy, lacking the expected targeting problems for lamin C and other proteins such as emerin. Only a minimal alteration in nuclear shape was present in the cell; this problem was not seen, however, in Lmna$^{LCO/-}$ cells. Fong et al. (2006) also found that lamin A is not required for the targeting of either lamin C or emerin to the nuclear envelope in mouse fibroblasts as previously thought. This suggests that lamin A and prelamin A are in fact dispensable to the cell; however, this does not mean these proteins are without purpose.

With this information, Fong et al. (2006) then used gene therapy as a treatment for Zmpste24$^{-/-}$ mice. They found that even a single Lmna^{LCO} allele eliminated the disease phenotypes normally seen in these knockout mice, including osteolytic lesions in bones, alopecia, and reduced subcutaneous fat. The scientists suggest that the physiological function of prelamin A, which is currently unknown, could be relatively unimportant from the perspective of a progeria patient.
Additionally, Scaffidi and Mistelli (2005) suggest that simply correcting the appearance of a cryptic splice site on the mRNA coding region for the prelamin A protein

by using a morpholino oligonucleotide would reverse detrimental cell morphology. In doing so, this artificial sequence overrides the original DNA sequence containing the point mutation, thus allowing for the translation of the complete sequence for the prelamin A protein (Scaffidi & Mistelli, 2005). The use of this morphino oligonucleotide sequence did not affect the amount of wild-type lamin A produced in protein synthesis; however, levels of progerin/LAΔ50 were completely diminished (Scaffidi & Mistelli, 2005). In relation to the decrease of progerin/LAΔ50, the nuclei of HGPS cells were observed to have less nuclear blebbing, suggesting that correction of the alternative splice site restores the cell to its normal morphology and potentially would correct the diseased phenotypes observed in HGPS patients (Scaffidi & Mistelli, 2005).

Conclusion

Hutchinson-Gilford Progeria Syndrome and Restrictive Dermopathy are caused by a disruption in the pathway in which lamin A is formed from prelamin A. The cause of HGPS was unknown until 2003 when Eriksson et al. identified a mutation in the LMNA gene. The resulting 50 amino acid deletion prevents the formation of mature lamin A.

Furthermore, in 2004, Navarro et al. discovered a common mutation in exon 9 of the Zmpste24 gene in RD patients. Consequently, the normal Zmpste24 enzyme is not produced and cannot function to create mature lamin A. Although the Zmpste24 mutation is a major component of RD, it must either be a homozygous mutation or be paired with another mutation within the ZMPSTE24 gene. Scientists have yet to discover the additional mutations that contribute to this disease.

In both HGPS and RD, studies have shown that the aforementioned mutations cause changes in cellular architecture and disruption of the cell cycle. This results in phenotypes of premature aging and early death.

Current treatments used in clinical trials include gene therapy and the use of farnesyl-transferase inhibitors (FTIs). Despite the improvements seen in phenotypic expression, it would be pertinent for future studies to examine whether FTI treatment has a similar effect on HGPS patients that already suffer from advanced symptoms (Yang et al., 2006). One main drawback in FTI treatment, however, is the inability to target prelamin A farnesylation specifically. There are a number of proteins involved in essential cellular processes that undergo CAAX modification similar to that of prelamin A, and thus could be affected as well. Further studies regarding the possible toxicity of prelamin A and its cumulative effects on the cell are also necessary.

With continued research, more knowledge can be gained about the normal aging process. This, in turn, could be applied to understanding progeroid syndromes in order to develop alternative treatments for these devastating pediatric diseases.

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