

Can a mixture of micronutrients delay the onset and progression of Hutchinson-Gilford Progeria syndrome?

Kedar N Prasad ^{1,*} and Stephen C. Bondy ²

¹ Engage Global, Inc, 245 El Faisan Drive, San Rafael, CA 94903.

² Center for Occupational and Environmental Health, University of California, Irvine, CA 92697.

World Journal of Biology Pharmacy and Health Sciences, 2022, 10(03), 073–081

Publication history: Received on 14 May 2022; revised on 22 June 2022; accepted on 24 June 2022

Article DOI: <https://doi.org/10.30574/wjbphs.2022.10.3.0081>

Abstract

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare autosomal dominant genetic disorder of accelerated aging caused by a point mutation in LMNA gene coding for a nuclear protein Lamin A which maintains normal structure and function of the nucleus. Mutated Lamin A protein undergoes a series of enzymatic modifications including farnesylation and prenylation to form a toxic protein progerin that alters nuclear structure and function. HGPS disease begins *in utero*; however, infants appear normal at birth with some features such as circumoral pallor. The expression of progerin is low in undifferentiated cells which may account for the fewer symptoms of progeria. In about 9-12 months, the levels of progerin in cells become high enough to produce nuclear structure abnormalities leading to cellular and molecular damages characteristic of HGPS. The average age of these patients is 14.6 years. Some therapeutic agents were developed by inhibiting a specific target, such as transcriptional activity, post-translation enzymatic steps, autophagy, and oxidative stress. These agents were tested in experimental models of cells of progeria yielding a modest improvements in phenotypes and slight extension of the lifespan of progeria patients. Since oxidative stress and chronic inflammation are involved in pathogenesis of progeria, this review proposes that a combination of a mixture of micronutrients with currently used therapeutic approaches may extend the life-span more than that produced by drug therapy alone.

Keywords: Progeria; Mutation in LMNA gene; Accelerated aging; oxidative stress; Micronutrient mixture

1. Introduction

The word progeria is derived from Greek word “progeros” means prematurely old. A point mutation in a nuclear LMNA gene, which codes for proteins lamin A and C, causes Hutchinson-Gilford progeria syndrome (HGPS, also called progeria). Intermediate filament proteins lamin A and C provide shape and mechanical stability of cells by supporting components of the nuclear envelop which surrounds the nucleus. They exhibit multiple functions including regulation of gene expression, DNA replication, DNA damage and repair, telomere protection, chromatin organization, and cell differentiation (1). Therefore, any defect in lamin protein could have serious consequences for the cells leading to senescence and ultimately death.

Mutation in LMNA gene causes prelamin A to undergo several post-translational modifications which include farnesylation by the farnesyltransferase (FTase), cleaving by metallopeptidase, and then carboxymethylation by the enzyme isoprenylcysteine carboxyl methyltransferase (ICMT) leading to the formation of truncated toxic form of protein called progerin which is irreversibly farnesylated and carboxyl methylated. Progerin accumulates in the nucleus causing abnormal nuclear morphology (2, 3). HGPS disease processes begin *in utero*; however, infants with HGPS

* Corresponding author: Kedar N Prasad
Engage Global, Inc, 245 El Faisan Drive, San Rafael, CA 94903.

appeared normal at birth and have normal birth weight, but some features such as circumoral pallor, are present at birth. This mild phenotype of the diseases may be due to the fact that the expression of progerin is low in undifferentiated cells. In about 9-12 months, the levels of progerin in cells increase high enough to initiate changes in nuclear morphology and associated metabolic abnormalities characteristics of HGPS as well as pathological and behavior signs of accelerated aging, which is characterized by loss of hair, and subcutaneous fat, atherosclerosis, myocardial infarction, and stroke. These changes lead to death at an average age of 14.6 years (4). HGPS is a rare autosomal dominant genetic disorder affecting 1 in every 4-8 million children (5).

In patients with HGPS, function of some organs is markedly impaired. Damage to the skin and hair, including alopecia, prominent superficial veins, and depigmentation are present before the age of 24 months (6). However, other organs such as the brain and immune system are much less affected (7). The brain is protected in progeria patients, since protein lamin A is not present in the brain at high levels. This is due to presence of miR-9, a brain specific microRNA, which decreases the rate of translation of lamin A protein from its mRNA leading to a reduction in the levels of progerin (8).

Increased expression of toxic protein progerin is also found in normal human cutaneous skin during aging (9). Low levels of progerin were found in tissues and cells of younger humans. It was further shown that the levels of progerin in the cells were not elevated during aging in the absence of shortening of telomeres. This implied a close relationship between elevated progerin levels and telomere attrition during aging (10). The fibroblasts from normal subjects aged 81-96 years old showed nuclear abnormalities similar to those found in the fibroblasts from patients with HGPS. In addition, the levels of heterochromatin, and heterochromatin protein (HP1) were decreased in both type of fibroblasts from normal old humans and from HGPS victims; however, the level of reduction was more pronounced in the HGPS fibroblasts than in the normally aged fibroblasts (11). This study also reported that DNA damage in the form of double-strand breaks was high in fibroblasts from both aged individuals and patients with HGPS. These results suggest that some mechanisms of normal aging and HGPS are similar. Production of progerin is a late event in normal aging processes, however, in progeria patients, progerin is produced as an early event. Therefore, experimental models of accelerated aging such as HGPS may not be useful for attenuating the rate of human normal aging.

Primary fibroblasts from HGPS patients has a reduced rate of proliferation and an enhancement of accelerated aging phenotypes (12). In addition, impaired DNA repair mechanism (13), increased ROS production (14), mitochondrial dysfunction (15), shortening of telomeres (16), and loss of peripheral chromatin were observed in these fibroblasts (17, 18).

Progerin impairs Nrf2 transcriptional activity by interfering its binding ability with ARE leading to decreased antioxidant enzymes and detoxifying enzymes (19) resulting into increased oxidative stress. Oxidative stress and chronic inflammation are closely linked. If oxidative damage is not repaired by products of acute inflammation, the consequent chronic inflammation can release further free radicals, pro-inflammatory cytokines, and complement proteins, all of which are toxic. Thus, increased oxidative stress and chronic inflammation may be targeted by antioxidants to reduce the rate of aging in patients with progeria.

Endothelial dysfunction is the key factor in the development of atherosclerosis which is an important concomitant of HGPS. Increased expression of progerin impairs human coronary endothelial cells in culture by increasing oxidative stress and inflammation associated with DNA damage, increased cell cycle arrest protein, and cellular senescence. Treatment HGPS cells with a combination of pravastatin and zoledronate, which inhibit prenylation, partly prevented these defects (20).

The efficacy of new therapeutic agents has been tested in HGPS fibroblasts or mesenchymal cells in culture. In order to develop these further it is essential to utilize animal models that can mimic the phenotypic features of accelerated aging of human HGPS. These models include a homozygous mouse model (LMNA^{G609G/G609G}) which appears to mimic many features of musculoskeletal and vascular alterations found in human HGPS . However this animal model does not develop atherosclerosis that is considered most the life-threatening component of HGPS (21). In consequence, another mouse model (Apoe^{-/-} LMNA^{G609G/G609G}) , which expressed progerin and exhibited premature aging associated with accelerated atherosclerosis similar to those of human HGPS has been developed (22). In addition to mouse models, a large animal model (LMNAc.1824C>T) Youcatan minipig has been established. This model exhibits the main features of human HGPS, such as production of progerin, retardation of growth, lipodystrophy, skin and bone alterations, cardiovascular disease, and mortality around puberty (23).

The objective of this review is to describe and evaluate the efficacy of therapeutic agents for the treatment of HGPS. These include use of inhibitors of transcriptional activity and enzymatic post-translation steps of progerin, and activator

of autophagy. The combination of two different agents was more effective than a single agent. In addition, a few individual antioxidants have been used to suppress progerin-induced oxidative stress. No studies have been performed to evaluate the efficacy of a combination of antioxidants with drugs focused on inhibition of individual metabolic steps in the management of progeria. This review proposes that oral administration of a comprehensive mixture of micronutrients in combination with more selective drugs might be the most effective means of delaying the onset and progression of HGPS.

2. Development of Therapeutic Agents for HGPS

Therapeutic approaches for treating HGPS have been recently reviewed(24)

Some examples are described here.

2.1. Inhibition of transcriptional activity based therapy

This therapy tested the ability of a number of antisense peptide-conjugated phosphorodiamidate morpholino oligomers to inhibit pathogenic splicing of mutant transcripts. Among them SRP2001 was found to most effective in reducing progerin levels in the fibroblasts of HGPS patients. Intravenous administration of SRP2001 produced significant reduction of progerin transcripts in the aorta of transgenic mouse model of progeria. Long-term continuous treatment with SRP2001 increased the lifespan of mice by 61.6%, and prevented loss of vascular smooth cells of large arteries (25). Another antisense oligonucleotide (LB143) markedly reduced progerin-producing mRNA in the transgenic model of progeria (26). The combination of antisense oligonucleotide and Zokinvy (Lonafarnib), an inhibitor of farnesyltransferase, was more effective in reducing the levels of progerin in the liver and heart than the individual agent alone (Progeria Research Foundation, 2021).

2.2. Post-translation based therapy

The FDA approved drug Lonafarnib remains one of the current treatment of HGPS. A combination of Lonafarnib, an inhibitor of farnesyltransferase that prevents progerin from combining with the inner nuclear membrane, together with Everolimus, an analog of rapamycin, which activates autophagy and thereby enhanced the removal of progerin (27), is in phase I/II trial (NC02579044). The utility of Lonafarnib in combination with Zoledronic acid or pravastatin is currently being studied.

Another drug progerinin is in a phase I trial (24). Treatment of HGPS fibroblasts in culture with progerinin, an optimized progerin-lamin A binding inhibitor (JH4) decreased the levels of progerin and improved nuclear defects. In the genetic mouse model of progeria, administration of progerinin enhanced body weight, and extended lifespan by 10 weeks compared to those treated with lonafarnib (28).

Treatment of fibroblasts from patients with HGPS with an inhibitor of S-isoprenylcysteine-O-methyltransferase (ICMT), the enzyme essential for the last step in post-translation processing progerin, decreased markers of accelerated aging and ROS, and enhanced proliferation of the cells (29).

Rapamycin, an immunosuppressive agent, activates autophagy, leading to improved nuclear shape and delayed onset of aging in HGPS fibroblasts (30, 31). Mice with deletion of the LMNA gene (-/-), are used as a model for dilated cardiomyopathy and muscular dystrophy. Treatment of these mice with rapamycin improved cardiac and skeletal muscle functions and enhanced survival by reversing of elevated target of rapamycin complex1 (mTORC1) signal (32). Using this genetic mouse model, treatment with rapamycin increased the lifespan, body weight, and fat contents (33). However, the changes found in mice with deleted LMNA (-/-) do not mimic the genetic and pathophysiology of HGPS in humans. In addition, rapamycin may be toxic for children and therefore, is thus unlikely to be of therapeutic value for patients with HGPS. However, Everolimus, an analog of rapamycin which activates autophagy, enhances the removal of progerin and has been suggested to have potential clinical benefit for multiple laminopathy syndromes including HGPS (27).

2.3. Oxidative stress based therapeutic agents

Progerin-induced oxidative stress is caused by impairing transcriptional ability of Nrf2 by preventing the binding of Nrf2 with ARE (antioxidant response element) (19). A similar impaired binding is found in aged rats and treatment with alpha-lipoic acid restores this binding ability (34).

Suppression of Nrf2 leads to changes, which resemble cellular defects observed in patients with HGPS. Re-activation of Nrf2 activity reversed progerin-induced nuclear abnormalities in the fibroblasts from patients with HGPS, and restored the viability of mesenchymal stem cells in genetic animal model of progeria. These results suggest that suppression of Nrf2 transcriptional ability is a major contributor to the premature aging phenotype (19).

Increased oxidative stress can cause impaired DNA repair mechanisms (13), mitochondrial dysfunction (15), shortening of telomeres (16), and autophagy defects (35-37). Therefore, attenuation of oxidative stress may delay the symptoms of progeria as well as its progression by improving above cellular defects. Antioxidants are known to reduce oxidative damage. Resveratrol, which exhibits antioxidant and anti-inflammatory effects, also activates autophagy in mouse model of diabetic neuropathy (38) and Hela cells (39). Thus administration of antioxidants may be of use as a supplementary strategy in improving the overall treatment of progeria. A few studies on the effects antioxidants in the treatment of progeria has been conducted. These studies are described here,

2.4. Application of Antioxidants or Vitamin D

Recent progress in therapies of HGPS has been reviewed (40). Treatment of HGPS fibroblasts in culture with n-acetylcysteine (NAC) restored their ability to repair DNA double-strand breaks, decreased population doubling time, and improved nuclear anomalies (41). Treatment of HGPS mesenchymal stem cells with vitamin C and/or quercetin inhibited production of progerin, age-related changes, and enhanced the ability of cell to proliferate (42). Resveratrol enhanced the SIRT1 deacetylase activity by enhancing the association between SIRT1 and Lamin A protein in the nucleus of wild-type cells; however this association was found to be disrupted in cells expressing progerin. Supplementation with resveratrol attenuated progeroid phenotypes and increased the lifespan in the *Zmpste24*^{-/-} mouse model of HGPS (43).

Vitamin D receptor knockout mice developed several phenotypes of HGPS, such as reduce lifespan and cardiovascular pathology (44, 45). Furthermore, HPGS cells have decreased levels of vitamin D receptor and DNA repair factors BRCA1 and 53BP1. In addition, treatment of HPGs cells with vitamin D attenuated some phenotypes, such as premature aging and DNA repair defects (46).

3. Problems Associated with the Use of a Single Antioxidant for Reducing Oxidative Stress in Patients with HGPS

While the administration of a single antioxidant appears to be effective in reducing some features of progeria in cell culture models, it may not be useful in delaying the onset or progression of HGPS in humans because of several problems. Some of them are described here.

- Patients with progeria exhibit increased levels of oxidative stress. Administration of a single antioxidant in a high internal oxidative environment of these patients could lead to its oxidation, which would further promote rather than inhibit free radical production.
- Different antioxidants are distributed differently in the sub-cellular compartments of cells, all of which must be protected from oxidative stress. Administration of a single antioxidant cannot accumulate in all parts of the cell in sufficient amounts to improve cellular defects associated with accelerated aging. Furthermore, Vitamin E is more effective scavenger of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher oxygen pressure of the cells (47). Therefore, administration of one antioxidant may not retard the progeria disease process.
- Simultaneous elevation of both antioxidant enzymes and dietary and endogenous antioxidant compounds are needed to achieve maximal reduction in oxidative stress. This is due to the fact that they act by different mechanisms. Antioxidant compounds neutralize free radicals by donating electrons to those molecules with unpaired electrons, whereas antioxidant enzymes destroy H₂O₂ and the superoxide radical by catalysis, converting them to harmless molecules such as water and oxygen. Administration of a single antioxidant cannot achieve this goal.
- Since most antioxidants are either lipophilic or hydrophilic, administration of a single antioxidant cannot protect both the aqueous and lipid compartments of the cell against oxidative damage.
- Different antioxidants activate Nrf2 in the cells by altering the expression of different microRNAs (48). For example, some antioxidants can activate Nrf2 by upregulating miR-200a that inhibits its target protein Keap1, whereas others activate Nrf2 by downregulating miR-21 that binds with 3'-UTR Nrf2 mRNA (49). Thus, different antioxidants activate Nrf2 (Nuclear Factor-Erythroid-2- Related Factor 2) by different mechanisms. Administration of a single antioxidant cannot act on all the relevant microRNAs.

- Administration of a single antioxidant compound in humans have often failed to yield expected benefits despite positive effects in experimental models. For example, administration of vitamin E alone produced no effect in patients with Parkinson's disease (50, 51). It also had no effect on cognitive function in patients with Alzheimer's disease, and produced minimal benefits in early phase of this disease (52, 53). Administration of beta-carotene alone in male heavy tobacco smokers increased the risk of lung cancer (54). These studies suggest that administration of a single antioxidant is unlikely to provide any significant improvement in patients with progeria.

4. Simultaneous Reduction of Oxidative Stress and Inflammation

In order to reduce oxidative stress and inflammation optimally, levels of intrinsic antioxidant enzymes should be increased together with intracellular concentrations of antioxidants (55). Oral supplementation with a mixture of antioxidants can increase the intracellular levels of antioxidant compounds; however, enhancing the content of antioxidant enzymes requires activation of the nuclear transcriptional factor Nrf2. A brief description of activation processes is presented here.

4.1. Processes of Activation of Nrf2

Under normal physiological conditions, activation of Nrf2, one of the nuclear transcriptional factors, requires ROS. Activated Nrf2 dissociates itself from Keap1- Cul-Rbx1 complex and migrates to the nucleus where it heterodimerizes with a small Maf protein and binds with ARE (antioxidant response element) leading to increased transcription of cytoprotective enzymes including antioxidant enzymes (56, 57). However, during prolonged oxidative stress commonly observed in human chronic diseases, activation of Nrf2 becomes resistant to ROS (58-60). This is evidenced by the fact that increased oxidative stress continues to occur in chronic diseases despite the presence of Nrf2. In the patients with progeria, increased oxidative stress occurs as soon as progerin is produced in the cells. This suggests that activation of Nrf2 becomes resistant to ROS.

In order to increase the levels of antioxidant enzymes, activated Nrf2 must bind to ARE to increase the transcription of cytoprotective enzymes, such as detoxifying enzymes and antioxidant enzymes. Progerin prevents the binding ability of Nrf2 with ARE (19). Similarly the binding ability of Nrf2 to ARE was impaired in aged rats but this defect was reversed by supplementation with alpha-lipoic acid (34).

Activation of Nrf2 decreases oxidative stress as well inflammation (61, 62). Many antioxidant compounds also attenuate inflammation (63-68). Treatment of HGPS cells with tocilizumab, a human monoclonal antibody, which neutralizes pro-inflammatory interleukin -6 (IL-6) receptor, reduced the levels of progerin and nuclear defects. In the genetic mouse model of progeria, tocilizumab treatment improved skin condition, weight, locomotor activity, and lifespan (69).

5. Proposed Mixture of Micronutrients in Combination with Other Therapeutic Approaches in the Treatment of HGPS

A comprehensive mixture of micronutrients containing vitamin A, mixed carotenoids, vitamin C, alpha-tocopheryl acetate, alpha-tocopheryl succinate, vitamin D3, alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, quercetin, all B-vitamins, and minerals selenomethionine, and zinc for prevention and management of neurodegenerative diseases has been proposed (55, 70). This mixture would increase the levels of antioxidant enzymes by restoring the ability of Nrf2 to bind with ARE and increasing the intracellular concentrations of antioxidant compounds. Such a micronutrient mixture may most effectively reduce oxidative stress and chronic inflammation as well as activate autophagy. This micronutrient mixture in combination with other therapeutic approaches may delay the onset and progression HGPS. Since early sign of progeria can be detected in utero, treatment with the micronutrient mixture alone in combination with other non-toxic approaches may best be initiated during pregnancy soon after detection of this development abnormalities.

Two clinical studies support the value of a mixture of micronutrient in producing beneficial effects in certain human diseases in which oxidative stress and inflammation plays a major role in their pathogenesis. For example, administration of multiple micronutrients reduced the risk of cancer in men (71) and delayed the progression of HIV disease by prolonging the time period for initiating the anti-viral therapy (72). Therefore, it is to be expected that the proposed micronutrient mixture may delay the onset of progeria when administered *in utero*.

6. Conclusion

Progeria is essentially an untreatable disease and although some of the sequelae of the disorder have been pharmacologically ameliorated, no reliable means of extending the short life expectancy of patients has hitherto been developed. The extreme rarity of the disease has not permitted comparative clinical trials and thus most research has been confined to *ex vivo* studies with isolated systems. These provide good mechanistic understanding but their role in developing novel therapies have been limited. A rationale is given here for nutritional supplementation of HGPS patients with a blend of antioxidants and other dietary components active in promoting intermediary metabolism. Such a mixture might be of use in delaying the progression of the disease especially when combined with agents more specifically targeted to impacting on the gene expression of the mutant LMNA gene and consequent metabolism of the abnormal Lamin A variant. Such dietary addition can provide an optimal intracellular milieu within which more selective drugs can best function. Most of the constituents listed have previously been advocated as a means of decelerating normal aging. The components of the supplement discussed here are all found naturally and have often been shown to be of nutritional value. In addition, these materials are known to be non-toxic and non-carcinogenic at levels where they are generally used. Thus the potential benefit of adding such materials to a therapeutic treatment regimen for HGPS, far outweighs any potential adverse effect. Their ready availability and minimal cost are further positive attributes. Overall, our recommendation presents a risk-free tactic in contending with this disorder.

Compliance with ethical standards

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sector

Disclosure of conflict of interest

No conflict of interest.

References

- [1] Dubik N, Mai S. Lamin A/C: Function in Normal and Tumor Cells. *Cancers (Basel)*. 2020;12(12):3688
- [2] Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, et al. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci U S A*. 2004;101(24):8963-8968.
- [3] Scaffidi P, Misteli T. Lamin A-dependent nuclear defects in human aging. *Science*. 2006;312(5776):1059-1063.
- [4] Gonzalo S, Kreienkamp R, Askjaer P. Hutchinson-Gilford Progeria Syndrome: A premature aging disease caused by LMNA gene mutations. *Ageing Res Rev*. 2017;33:18-29.
- [5] Harhour K, Frankel D, Bartoli C, Roll P, De Sandre-Giovannoli A, Levy N. An overview of treatment strategies for Hutchinson-Gilford Progeria syndrome. *Nucleus*. 2018;9(1):246-257.
- [6] Rork JF, Huang JT, Gordon LB, Kleinman M, Kieran MW, Liang MG. Initial cutaneous manifestations of Hutchinson-Gilford progeria syndrome. *Pediatr Dermatol*. 2014;31(2):196-202.
- [7] Kreienkamp R, Gonzalo S. Metabolic Dysfunction in Hutchinson-Gilford Progeria Syndrome. *Cells*. 2020;9(2):395
- [8] Jung HJ, Coffinier C, Choe Y, Beigneux AP, Davies BS, Yang SH, et al. Regulation of prelamin A but not lamin C by miR-9, a brain-specific microRNA. *Proc Natl Acad Sci U S A*. 2012;109(7):E423-431.
- [9] Verdy C, Branka JE, Mekideche N. Quantitative assessment of lactate and progerin production in normal human cutaneous cells during normal ageing: effect of an *Alaria esculenta* extract. *Int J Cosmet Sci*. 2011;33(5):462-466.
- [10] Cao K, Blair CD, Faddah DA, Kieckhafer JE, Olive M, Erdos MR, et al. Progerin and telomere dysfunction collaborate to trigger cellular senescence in normal human fibroblasts. *J Clin Invest*. 2011;121(7):2833-2844.
- [11] Ashapkin VV, Kutueva LI, Kurchashova SY, Kireev, II. Are There Common Mechanisms Between the Hutchinson-Gilford Progeria Syndrome and Natural Aging? *Front Genet*. 2019;10:455.
- [12] Huang S, Chen L, Libina N, Janes J, Martin GM, Campisi J, et al. Correction of cellular phenotypes of Hutchinson-Gilford Progeria cells by RNA interference. *Hum Genet*. 2005;118(3-4):444-450.

- [13] Manju K, Muralikrishna B, Parnaik VK. Expression of disease-causing lamin A mutants impairs the formation of DNA repair foci. *J Cell Sci.* 2006;119(Pt 13):2704-2714.
- [14] Viteri G, Chung YW, Stadtman ER. Effect of progerin on the accumulation of oxidized proteins in fibroblasts from Hutchinson Gilford progeria patients. *Mech Ageing Dev.* 2010;131(1):2-8.
- [15] Rivera-Torres J, Acin-Perez R, Cabezas-Sanchez P, Osorio FG, Gonzalez-Gomez C, Megias D, et al. Identification of mitochondrial dysfunction in Hutchinson-Gilford progeria syndrome through use of stable isotope labeling with amino acids in cell culture. *J Proteomics.* 2013;91:466-477.
- [16] Decker ML, Chavez E, Vulto I, Lansdorp PM. Telomere length in Hutchinson-Gilford progeria syndrome. *Mech Ageing Dev.* 2009;130(6):377-383.
- [17] McCord RP, Nazario-Toole A, Zhang H, Chines PS, Zhan Y, Erdos MR, et al. Correlated alterations in genome organization, histone methylation, and DNA-lamin A/C interactions in Hutchinson-Gilford progeria syndrome. *Genome Res.* 2013;23(2):260-269.
- [18] Columbaro M, Capanni C, Mattioli E, Novelli G, Parnaik VK, Squarzone S, et al. Rescue of heterochromatin organization in Hutchinson-Gilford progeria by drug treatment. *Cell Mol Life Sci.* 2005;62(22):2669-2678.
- [19] Kubben N, Zhang W, Wang L, Voss TC, Yang J, Qu J, et al. Repression of the Antioxidant NRF2 Pathway in Premature Aging. *Cell.* 2016;165(6):1361-1374.
- [20] Bidault G, Garcia M, Capeau J, Morichon R, Vigouroux C, Bereziat V. Progerin Expression Induces Inflammation, Oxidative Stress and Senescence in Human Coronary Endothelial Cells. *Cells.* 2020;9(5):1201
- [21] Cubria MB, Suarez S, Masoudi A, Oftadeh R, Kamalpathy P, DuBose A, et al. Evaluation of musculoskeletal phenotype of the G608G progeria mouse model with lonafarnib, pravastatin, and zoledronic acid as treatment groups. *Proc Natl Acad Sci U S A.* 2020;117(22):12029-12040.
- [22] Osmanagic-Myers S, Kiss A, Manakanatas C, Hamza O, Sedlmayer F, Szabo PL, et al. Endothelial progerin expression causes cardiovascular pathology through an impaired mechanoresponse. *J Clin Invest.* 2019;129(2):531-545.
- [23] Dorado B, Ploen GG, Baretino A, Macias A, Gonzalo P, Andres-Manzano MJ, et al. Generation and characterization of a novel knockin minipig model of Hutchinson-Gilford progeria syndrome. *Cell Discov.* 2019;5:16.
- [24] Macicior J, Marcos-Ramiro B, Ortega-Gutierrez S. Small-Molecule Therapeutic Perspectives for the Treatment of Progeria. *Int J Mol Sci.* 2021;22(13).
- [25] Erdos MR, Cabral WA, Tavarez UL, Cao K, Gvozdenovic-Jeremic J, Narisu N, et al. A targeted antisense therapeutic approach for Hutchinson-Gilford progeria syndrome. *Nat Med.* 2021;27(3):536-545.
- [26] Puttaraju M, Jackson M, Klein S, Shilo A, Bennett CF, Gordon L, et al. Systematic screening identifies therapeutic antisense oligonucleotides for Hutchinson-Gilford progeria syndrome. *Nat Med.* 2021;27(3):526-535.
- [27] DuBose AJ, Lichtenstein ST, Petrash NM, Erdos MR, Gordon LB, Collins FS. Everolimus rescues multiple cellular defects in laminopathy-patient fibroblasts. *Proc Natl Acad Sci U S A.* 2018;115(16):4206-4211.
- [28] Kang SM, Yoon MH, Ahn J, Kim JE, Kim SY, Kang SY, et al. Progerinin, an optimized progerin-lamin A binding inhibitor, ameliorates premature senescence phenotypes of Hutchinson-Gilford progeria syndrome. *Commun Biol.* 2021;4(1):5.
- [29] Ibrahim MX, Sayin VI, Akula MK, Liu M, Fong LG, Young SG, et al. Targeting isoprenylcysteine methylation ameliorates disease in a mouse model of progeria. *Science.* 2013;340(6138):1330-1333.
- [30] Cao K, Graziotto JJ, Blair CD, Mazzulli JR, Erdos MR, Krainc D, et al. Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells. *Sci Transl Med.* 2011;3(89):89ra58.
- [31] Graziotto JJ, Cao K, Collins FS, Krainc D. Rapamycin activates autophagy in Hutchinson-Gilford progeria syndrome: implications for normal aging and age-dependent neurodegenerative disorders. *Autophagy.* 2012;8(1):147-151.
- [32] Ramos FJ, Chen SC, Garelick MG, Dai DF, Liao CY, Schreiber KH, et al. Rapamycin reverses elevated mTORC1 signaling in lamin A/C-deficient mice, rescues cardiac and skeletal muscle function, and extends survival. *Sci Transl Med.* 2012;4(144):144ra03.

- [33] Liao CY, Anderson SS, Chicoine NH, Mayfield JR, Academia EC, Wilson JA, et al. Rapamycin Reverses Metabolic Deficits in Lamin A/C-Deficient Mice. *Cell Rep.* 2016;17(10):2542-2552.
- [34] Suh JH, Shenvi SV, Dixon BM, Liu H, Jaiswal AK, Liu RM, et al. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. *Proc Natl Acad Sci U S A.* 2004;101(10):3381-3386.
- [35] Filomeni G, Desideri E, Cardaci S, Rotilio G, Ciriolo MR. Under the ROS...thiol network is the principal suspect for autophagy commitment. *Autophagy.* 2010;6(7):999-1005.
- [36] Chen Y, Azad MB, Gibson SB. Superoxide is the major reactive oxygen species regulating autophagy. *Cell Death Differ.* 2009;16(7):1040-1052.
- [37] Scherz-Shouval R, Shvets E, Elazar Z. Oxidation as a post-translational modification that regulates autophagy. *Autophagy.* 2007;3(4):371-373.
- [38] Huang SS, Ding DF, Chen S, Dong CL, Ye XL, Yuan YG, et al. Resveratrol protects podocytes against apoptosis via stimulation of autophagy in a mouse model of diabetic nephropathy. *Sci Rep.* 2017;7:45692.
- [39] Park D, Jeong H, Lee MN, Koh A, Kwon O, Yang YR, et al. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. *Sci Rep.* 2016;6:21772.
- [40] Lai WF, Wong WT. Progress and trends in the development of therapies for Hutchinson-Gilford progeria syndrome. *Aging Cell.* 2020;19(7):e13175.
- [41] Richards SA, Muter J, Ritchie P, Lattanzi G, Hutchison CJ. The accumulation of un-repairable DNA damage in laminopathy progeria fibroblasts is caused by ROS generation and is prevented by treatment with N-acetyl cysteine. *Hum Mol Genet.* 2011;20(20):3997-4004.
- [42] Geng L, Liu Z, Zhang W, Li W, Wu Z, Wang W, et al. Chemical screen identifies a geroprotective role of quercetin in premature aging. *Protein Cell.* 2019;10(6):417-435.
- [43] Liu B, Ghosh S, Yang X, Zheng H, Liu X, Wang Z, et al. Resveratrol rescues SIRT1-dependent adult stem cell decline and alleviates progeroid features in laminopathy-based progeria. *Cell Metab.* 2012;16(6):738-750.
- [44] Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev.* 2008;29(6):726-776.
- [45] Keisala T, Minasyan A, Lou YR, Zou J, Kalueff AV, Pyykkö I, et al. Premature aging in vitamin D receptor mutant mice. *J Steroid Biochem Mol Biol.* 2009;115(3-5):91-97.
- [46] Kreienkamp R, Croke M, Neumann MA, Bedia-Diaz G, Graziano S, Dusso A, et al. Vitamin D receptor signaling improves Hutchinson-Gilford progeria syndrome cellular phenotypes. *Oncotarget.* 2016;7(21):30018-30031.
- [47] Vile GF, Winterbourn CC. Inhibition of adriamycin-promoted microsomal lipid peroxidation by beta-carotene, alpha-tocopherol and retinol at high and low oxygen partial pressures. *FEBS Lett.* 1988;238(2):353-356.
- [48] Prasad KN, Bondy SC. MicroRNAs in Hearing Disorders: Their Regulation by Oxidative Stress, Inflammation and Antioxidants. *Front Cell Neurosci.* 2017;11:276.
- [49] Wu H, Kong L, Tan Y, Epstein PN, Zeng J, Gu J, et al. C66 ameliorates diabetic nephropathy in mice by both upregulating NRF2 function via increase in miR-200a and inhibiting miR-21. *Diabetologia.* 2016;59(7):1558-1568.
- [50] Shoulson I. DATATOP: a decade of neuroprotective inquiry. Parkinson Study Group. Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism. *Ann Neurol.* 1998;44(3 Suppl 1):S160-166.
- [51] Group TPS. Effect of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1993;328:176-183.
- [52] Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med.* 1997;336(17):1216-1222.
- [53] Isaac MG, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev.* 2008;(3):CD002854.
- [54] Alpha-Tocopherol B-CCPSG. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med.* 1994;330:1029-1035.

- [55] Prasad KN, Bondy SC. Inhibition of early upstream events in prodromal Alzheimer's disease by use of targeted antioxidants. *Curr Aging Sci*. 2014;7(2):77-90.
- [56] Hashimoto M, Yoshimoto M, Sisk A, Hsu LJ, Sundsmo M, Kittel A, et al. NACP, a synaptic protein involved in Alzheimer's disease, is differentially regulated during megakaryocyte differentiation. *Biochem Biophys Res Commun*. 1997;237(3):611-616.
- [57] Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB, et al. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst*. 2006;98(4):245-254.
- [58] Ramsey CP, Glass CA, Montgomery MB, Lindl KA, Ritson GP, Chia LA, et al. Expression of Nrf2 in neurodegenerative diseases. *J Neuropathol Exp Neurol*. 2007;66(1):75-85.
- [59] Chen PC, Vargas MR, Pani AK, Smeyne RJ, Johnson DA, Kan YW, et al. Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: Critical role for the astrocyte. *Proc Natl Acad Sci U S A*. 2009;106(8):2933-2938.
- [60] Lastres-Becker I, Ulusoy A, Innamorato NG, Sahin G, Rabano A, Kirik D, et al. alpha-Synuclein expression and Nrf2 deficiency cooperate to aggravate protein aggregation, neuronal death and inflammation in early-stage Parkinson's disease. *Hum Mol Genet*. 2012;21(14):3173-3192.
- [61] Kim J, Cha YN, Surh YJ. A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders. *Mutat Res*. 2010;690(1-2):12-23.
- [62] Li W, Khor TO, Xu C, Shen G, Jeong WS, Yu S, et al. Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis. *Biochem Pharmacol*. 2008;76(11):1485-1489.
- [63] Abate A, Yang G, Dennery PA, Oberle S, Schroder H. Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. *Free Radic Biol & Med*. 2000;29(11):1135-1142.
- [64] Fu Y, Zheng S, Lin J, Ryerse J, Chen A. Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. *Mol Pharmacol*. 2008;73(2):399-409.
- [65] Lee HS, Jung KK, Cho JY, Rhee MH, Hong S, Kwon M, et al. Neuroprotective effect of curcumin is mainly mediated by blockade of microglial cell activation. *Pharmazie*. 2007;62(12):937-942.
- [66] Rahman S, Bhatia K, Khan AQ, Kaur M, Ahmad F, Rashid H, et al. Topically applied vitamin E prevents massive cutaneous inflammatory and oxidative stress responses induced by double application of 12-O-tetradecanoylphorbol-13-acetate (TPA) in mice. *Chem Biol Interact*. 2008;172(3):195-205.
- [67] Suzuki YJ, Aggarwal BB, Packer L. Alpha-lipoic acid is a potent inhibitor of NF-kappa B activation in human T cells. *Biochem Biophys Res Commun*. 1992;189(3):1709-1715.
- [68] Zhu J, Yong W, Wu X, Yu Y, Lv J, Liu C, et al. Anti-inflammatory effect of resveratrol on TNF-alpha-induced MCP-1 expression in adipocytes. *Biochem Biophys Res Commun*. 2008;369(2):471-477.
- [69] Squarzone S, Schena E, Sabatelli P, Mattioli E, Capanni C, Cenni V, et al. Interleukin-6 neutralization ameliorates symptoms in prematurely aged mice. *Aging Cell*. 2021;20(1):e13285.
- [70] Prasad KN. Simultaneous activation of Nrf2 and elevation of antioxidant compounds for reducing oxidative stress and chronic inflammation in human Alzheimer's disease. *Mech Ageing Dev*. 2016;153:41-47.
- [71] Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308(18):1871-1880.
- [72] Baum MK, Campa A, Lai S, Sales Martinez S, Tsalaila L, Burns P, et al. Effect of micronutrient supplementation on disease progression in asymptomatic, antiretroviral-naive, HIV-infected adults in Botswana: a randomized clinical trial. *JAMA*. 2013;310(20):2154-2163.