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# The macromolecular machinery of the nucleus in the senescence process

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## Abstract

The different types of tissues of the human body age in different ways; Cells that undergo many divisions such epithelial and connective tissues if compared to neurons and muscle have different aging mechanisms. Thus, we propose a thesis that, cell nucleus is composed of a macrostructural machinery, whit mechanisms of control the number of mitotic divisions and chronological markers of cell age. So, the macro molecular proteins structures in telomeres called shelterin and proteins known as lamins that are core integrity conformational proteins of the nucleus would perform functions of cellular age as structural timers. Finally, in certain tissues an accumulation of a truncated lamin known as progerin and the shortening of telomeres in shelterin complex has a mechanical function in molecular machinery of the nucleus where they work a compression in the transcriptionally structure of active euchromatin, with advancing of age this compression would decrease the rate of transcription of many genes, and causing the aging of organism.

**Keywords:** Core molecular biology; Theories of aging; Mutations; Study models of aging

## 1. Introduction

Aging causes changes in molecular structure of cell nucleus and consequently in the rate of transcription of several genes including related to metabolism as DNA repair [1]. We can consider that there are cells that do not perform mitosis such as neurons [2], and muscle cells [3] but other tissues and organs such liver and epithelial connective tissue undergo many mitotic divisions, in this way we will consider the changes in the nuclear morphology off cells that undergo mitotic divisions, because in other categories of cells the oxidative theory is more elucidative.

The percentage media of nuclear DNA, RNA and protein were 28.8, 5.3 and 65.9 per cent respectively [4], which over 60% of core are proteins such as histones and many other responsible for the operation of nuclear machinery, so proteins are the main block of molecular machinery of the cell nucleus.

For example the telomeres are associated with several proteins, forming macro molecular structures complex in human telomeres called shelterin, a complex formed by six telomere-specific proteins associates with this sequence which protects chromosome ends, see the red circle in (figure-1 A) [5].

Another important protein that maintains the conformational integrity of the nucleus is lamin A; Some theories of aging claim that theoretically a truncated form of this protein called progerin would accumulate in the nucleus of certain tissues and organs. The progerin is a defective precursor of the lamin A nuclear matrix protein in which the C-terminal cysteine, which is removed normally, is retained and modified with a hydrophobic oligoisoprene chain .

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Thus the progerin molecules attach in inner membrane of the nuclear envelope, pushing away the adjacent fibrils of the nuclear matrix and the chromatin periphery. This changes the morphology and shape of the nucleus, alters the properties of the nuclear envelope and pore complexes.

As progerin accumulates, structural distortions increase in the nucleus, distorting the nuclear–cytoplasmic transport of macromolecules and leading to defects in cell metabolism [6]. This mechanism of aging has been identified in patients with Hutchinson–Gilford progeria syndrome (HGPS) [7,8].

In theory is possible that the accumulation of progerin and shortening of telomeres in shelterin complex has a mechanical function in molecular machinery of the cell nucleus exercising a mechanical compression in the structure transcriptionally of active euchromatin (Figure 1 B).

The animal cell has a standard mechanism for basic operation controlled by the gene sequence conserved for millions of years, this explains the fact that evolutionarily distant animals share percentages large of DNA sequences. For example: cats have 90% of homologous genes with humans, 82% with dogs, 80% with cows, 79% with chimpanzees, 69% with rats and 67% with mice [9,10,11] About 60% of chicken genes correspond to a similar human gene [12] and the fruit fly (Drosophila) shares about 60% of its DNA with humans [13].

Thus, the conservation of the DNA and consequently, their macro molecule machinery allows all animal cells a framework of operation in common; so, cumulative conformational changes in the basic core proteins as lanins and Shelterin protein complex generate a nucleus structural collapse known as cellular aging.

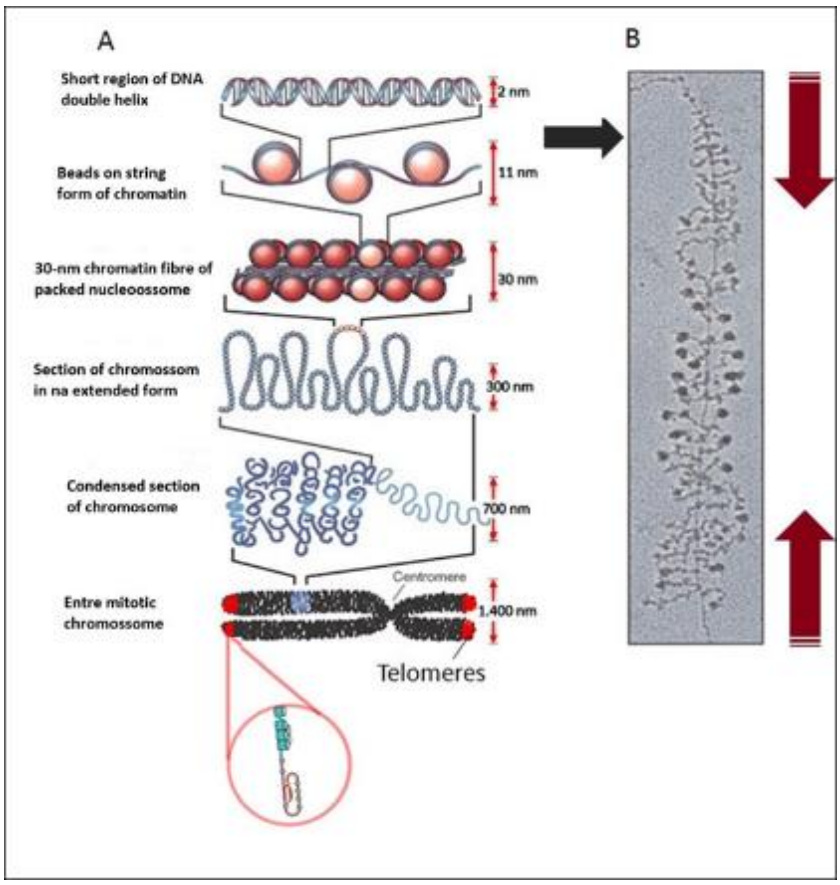


**Figure 1 (**A) shows an artistic representation of various level of DNA compaction. (B) The chromatosomes are disassembled by the action of RNA polymerase and the transcriptional region acquires the shape of a Christmas tree. In region of DNA between 11 and 2 nm (gray arrow), the nascent RNA gets bigger when approaches of the end; thus in this region the protein complex cuts and clamps for processing the primary transcript; so, a telomeric reduction theoretically cause a compression (red arrows direction) in this region causing a slowdown in process of primary transcript. Red arrows indicate the direction of compression in euchromatin caused by shortening of telomeres

### 1.1. Development

The nuclear lamina is a thin (10–20 nm) protein meshwork associated with the nuclear face of the inner nuclear membrane (INM) (Figure-2 A). Because of its role in maintaining nuclear envelope (NE) integrity and in providing anchoring sites for chromatin domains, the lamina is considered to represent an important determinant of interphase nuclear architecture. The major components of the lamina are intermediate filament-like proteins, the nuclear lamins [14].

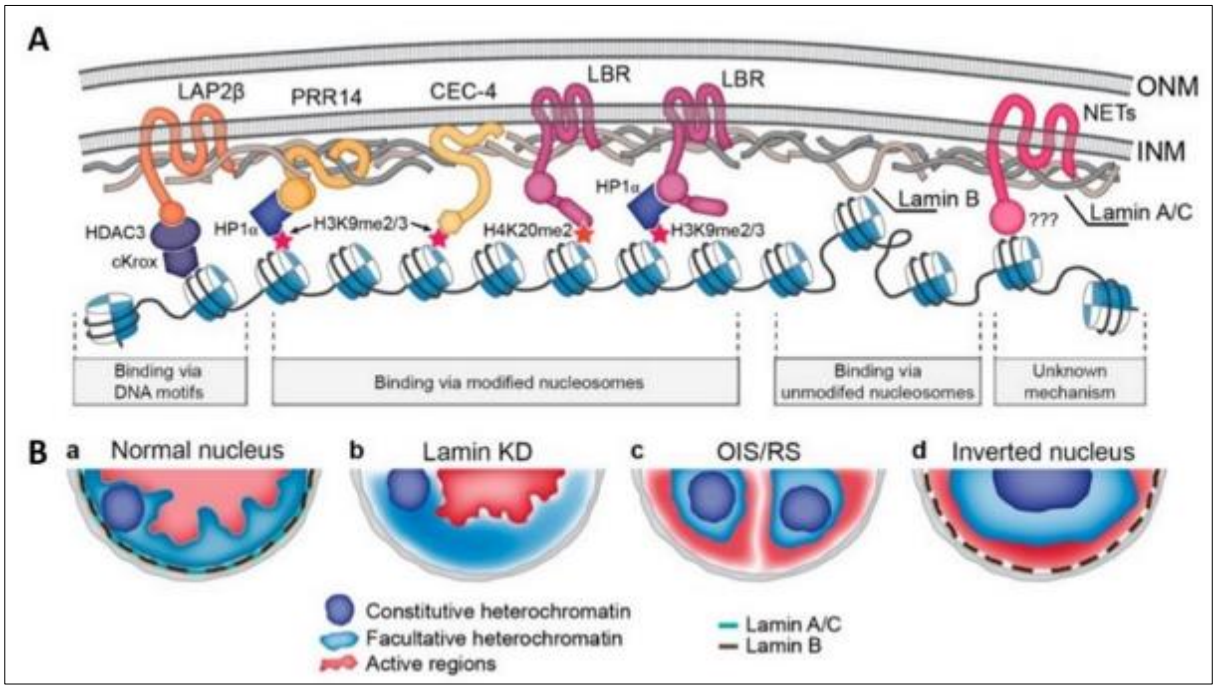


**Figure 2 (**A)Three types of nuclear lamina chromatin tethering mechanisms are summarized in schematic representation of the main nuclear lamina. (NE) Nuclear envelope. (NET) Nuclear envelope transmembrane protein Lap2β. (HDAC3) histone deacetylase.(cKrox) DNA-binding protein. (HP1α) Heterochromatin protein 1α. (H3K9me2/3) Histone H3 lysine 9 di/trimethylated. (H4K20me2) Histone H4 lysine 20 dimethylated. (B) Schematic representation of different types of chromosome architecture generated upon loss of NL-chromatin tethering. (a) Conventional nuclear architecture in most mammalian cell types. (b) Nuclear architecture in *Drosophila* S2 cells lacking both A- and B-type lamins. (c) Nuclear architecture upon oncogene-induced senescence (OIS) or replicative senescence (RS). (d) "Inverted" nuclear architecture in rod photoreceptors. Courtesy of (Shevelyov & Ulianov, 2019) by Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

HGPS laminopathies are caused mainly by mutations in the genes encoding the nuclear lamins, particularly in LMNA, the gene encoding lamins A and C, different LMNA mutations cause a wide range of diseases, including Hutchinson-Gilford Progeria Syndrome, Emery-Dreifuss Muscular Dystrophy, dilated cardiomyopathy, and lipodystrophy. Lamin B1 and B2 are two other isoforms encoded by LMNB1 and LMNB2, respectively, and are less frequently associated with diseases [15,16].

The lamins A and C are generated from the same gene, LMNA, by alternative splicing so mature lamin A differs from lamin C by a 74-aa C-terminal addition and is generated from a precursor prelamin A protein (Figure-3 A). Due to this processing mechanism, both isoforms lamin A and lamin C have a redundant role in the nuclear structure [17] demonstrating by mice that possessing only lamin C, but no lamin A or prelamin A, and because of this these animals are indistinguishable from wild-type mice (Figure-3 B).[18] this is curious because the absence of progerin in these animals does not contribute to an increase in their lifespan.

Thus, in animals we could think that absence of progerin does not increase life span but its presence causes morbidity, so if we extend this hypothesis to humans we could think that in normal humans lamins A and C have no effect on normal aging ; thereby, from this point, the theories presented that associate lamins with normal aging are hypothetical speculations.

Therefore, mutations in LMNA that affect only lamin A, but not lamin C, led to accumulation of the farnesylated prelamin A intermediate, which acts in a dominant fashion to cause HGPS. Thus, HGPS manifests in children who have no family pathological history related to this disease, so it is not an inherited disease; this mutation is thought to occur in a single sperm or egg immediately before conception [17].

In the mouse, A-type lamins do not appear until midway through embryonic development, suggesting that these proteins may be involved in the regulation of terminal differentiation [14]. Here mice lacking A/C-type lamins develop to term with no overt abnormalities however, their postnatal growth is severely retarded and is characterized by the appearance of muscular dystrophy (Figure-3 B) [14].

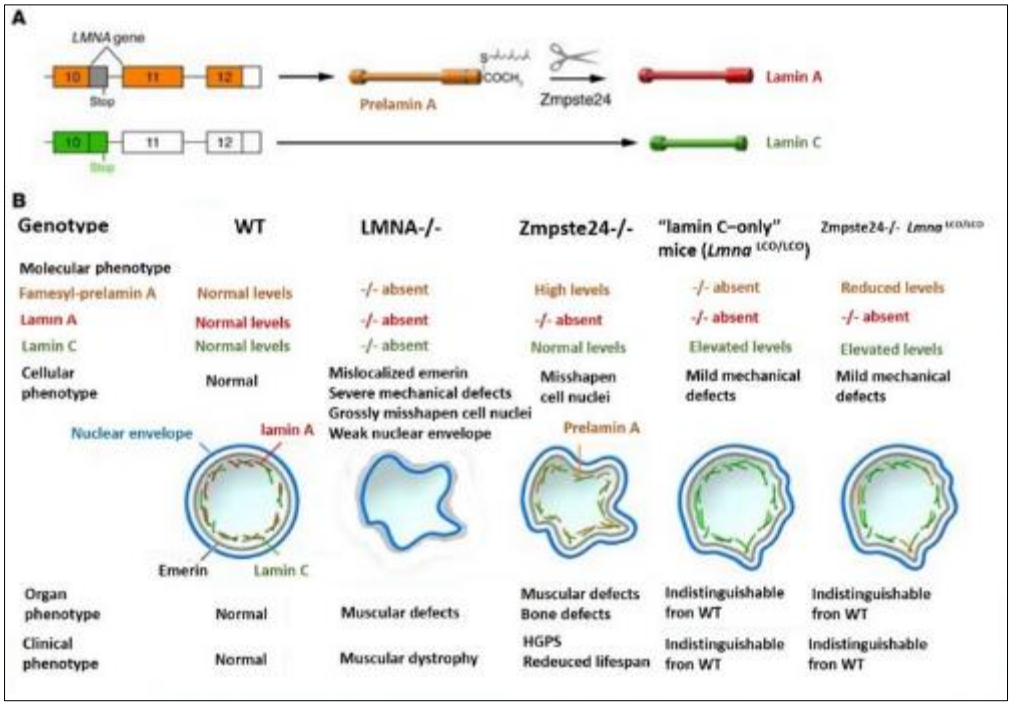


**Figure 3** Lamin A is not essential for a healthy mouse. (A) Lamin A and lamin C are generated by alternative splicing of the LMNA gene. Use of a donor splice site within exon 10 generates the prelamin A protein, which is then modified by farnesylation and subsequently cleaved by the Zmpste24 endoprotease to produce mature lamin A. Skipping of the exon 10 splice site generates lamin C. Due to the presence of a stop codon in exon 10, lamin C lacks the posttranslationally modified C-terminal region. (B) Comparison between cellular and organismal phenotypes in different mouse backgrounds. Courtesy of ( Scaffidi & Misteli, 2006) Copyright by American Society for Clinical Investigation

Analysis of the gene structure of A-and B-type lamins in conjunction with their pattern of expression in vertebrates led to the assumption that B-type lamins represent the ancestral type of lamins [19] so knockout animals in B-type lamins LMNB2-knockout mice (LMNB2−/−) suffer severe abnormalities; thereby absence of either lamin B1 or lamin B2, or the absence of both B-type lamins, results in severe neurodevelopmental abnormalities [20].

Thus, to talk about the macro structure of nuclear machinery we have to unite both Shelterin in the role of chromosomal telomeric structures and lamins proteins associated with face of nuclear membrane.

## 2. Discussion

The problem in defining which factors are relevant in the aging process is the fact that the human organism contains many types of tissues and the metabolic rate as well as the rate of mitotic division are varied.

In the human body there are four types of tissues: epithelia, connective (adipose, cartilaginous, bone and blood), muscle tissue (smooth, skeletal and cardiac) and nervous tissue. In this way we would have different processes of senescence happening. For example, in different tissues like epithelium and neurons, in the first mitotic divisions undergoes practically continuously, while the neurons do not undergo mitosis [2].

Another example is that most tumors originate from epithelial and connective tissues because of the high rate of mitotic division in these tissues [21]. Basically, according to their function these tissues are programmed to renew themselves practically continuously, and for that their metabolism is also accelerated, thus theoretically the epithelium and connective tissues degrades most rapidly with aging. In addition, the process of decrepitude and death by age involves the loss of muscle mass and reflexes, in addition to changes in hormonal rates, among other symptoms.

Therefore, when we address only one molecular mechanism of the senescence process, we have to be aware that this mechanism is just one piece of this puzzle known as aging.

In HGPS the disease firstly involves premature aging and then death from complications of atherosclerosis such as myocardial infarction, stroke, atherosclerosis, or heart failure which demonstrates the rapid degradation of the various types of epithelial and connective tissues in these patients [22, 23]. So, the lifespan of the patient is normally up to teen age or early twenties. It is usually not inherited because a patient normally dies before the age of reproduction, the absence of complete sexual maturation has been considered characteristic of the syndrome, but a HGPS girl delivered a normal child at the age of 23 [24] this fact could also show that HGPS syndrome can have moderate levels of morbidities.

The most important genetic linkage between progeria and aging is shortening of telomere ends with each replication cycle; thus patients are normally observed to have extremely short telomeres [25, 26] and was shown that telomerase therapy reverses vascular senescence and extends lifespan in progeria mice [27].

The mutations and diseases shown in (TABLE 1) demonstrate exacerbated symptoms of the senescence process, which in normal individuals happens like a mosaic in a gradual and dosed way, in addition, the senescence mechanisms are varied in different tissues of the same organism, in different individuals and in different species.

**Table 1** Mutations that cause premature ageing syndromes

| **Syndrome** | **Gene** | **Main function of gene** | **Symptoms** | **Non-represented chronic ageing diseases** | **Parallel with leading chronic ageing diseases** |
|---|---|---|---|---|---|
| Hutchinson-Gilford progeria syndrome | LMNA | Nuclear envelope architectural protein, heterochromatin organization | Alopecia, atherosclerosis, growth retardation, loss of subcutaneous fat, skeletal muscle wasting, nail dystrophy, stiff joints, tight skin, subcutaneous calcifications, osteoporosis, loss of eyesight, kidney failure | Cancer, CKD, COPD, diabetes, neurodegenerative diseases | Atherosclerosis, heart failure, skeletal muscle wasting, osteoporosis |
| Nestor-Guillermo progeria syndrome | *BANF1* | Nuclear envelope architectural protein, heterochromatin organization | Alopecia, growth retardation, loss of subcutaneous fat, skeletal muscle wasting, stiff joints, osteoporosis | Atherosclerosis, cancer, CKD, COPD, diabetes, heart failure, neurodegenerative diseases | Osteoporosis, skeletal muscle wasting |
| Werner syndrome | *WRN* (classical), *LMNA* (atypical) | *WRN:* DNA repair (NER, BER, NHEJ, HR), telomere maintenance | Growth retardation, tight skin, skin ulcers, osteoporosis, cataract, cardiac valve and soft tissue calcification, loss of subcutaneous fat, decreased fertility, increased risk for cancer | Cancer, CKD, COPD, diabetes, neurodegenerative diseases, skeletal muscle wasting, diabetes | Atherosclerosis, increased risk for cancer, heart failure, osteoporosis |

| | | | | | |
|---|---|---|---|---|---|
| Cockayne syndrome | *ERCC6, ERCC8* | DNA repair (NER) | Growth retardation, impaired development of the nervous system and progressive neurodegeneration, photosensitivity, cataracts | Atherosclerosis, cancer, CKD, COPD, diabetes, heart failure, osteoporosis, skeletal muscle wasting | Progressive neurodegeneration |
| Bloom syndrome | *BLM* | Double-strand break DNA repair | Growth retardation, photosensitivity, micrognathism, skin rash, dilated blood vessels, moderate immune deficiency, cancer, increased risk diabetes and COPD | Atherosclerosis, CKD, heart failure, osteoporosis, neurodegenerative diseases, skeletal muscle wasting | Cancer, increased risk for diabetes and COPD |
| Xeroderma pigmentosum | *XPA, XPB, XPC*, *XPD*, *XPG*, *ERCC 4*, *ERCC6*, *DDB2*, *POL H*, *RAD2* | DNA repair (NER) | Photosensitivity, cancer, dilated blood vessels | Atherosclerosis, CKD, COPD, diabetes, heart failure, osteoporosis, neurodegenerative diseases, skeletal muscle wasting | Cancer |
| Ataxia telangiectasia | *ATM* | DNA damage signaling activator | Growth retardation, weakened immune system, cancer, degeneration of cerebellum, dilated blood vessels, diabetes | Atherosclerosis, CKD, COPD, diabetes, heart failure, osteoporosis, skeletal muscle wasting | Cancer, diabetes, neuronal degeneration |
| Trichothiodystrophy | *XPB, XPD, TFB5* | DNA repair (NER) | Growth retardation, brittle hair, nail dystrophy, intellectual impairment, neuronal degeneration, reduced fertility | Atherosclerosis, cancer, CKD, COPD, diabetes, heart failure, osteoporosis, skeletal muscle wasting, diabetes | Neuronal degeneration |
| Dyskeratosis congenita | *TERC, TERT, CTC1*, *WRA P53* | Components of telomerase and telomere maintenance complex | Nail dystrophy, leukoplakia of oral mucosa, bone marrow failure, hyperpigmentation of skin, premature greying of hairs, testicular atrophy, cancer, osteoporosis, pulmonary fibrosis | Atherosclerosis, CKD, diabetes, heart failure, neurodegenerative diseases, skeletal muscle wasting | Cancer, osteoporosis, pulmonary fibrosis |
| Mosaic variegated aneuploidy syndrome | *BUB1B, CEP57* | Mitotic non-disjunction | Short stature, central nervous system and brain abnormalities, intellectual disability, aneuploidy, increased cancer risk, cataracts | Atherosclerosis, CKD, COPD, diabetes, heart failure, osteoporosis, neurodegenerative diseases, skeletal muscle wasting | Cancer |

So, the study of human ageing has been facilitated by the discovery of mutations that cause premature ageing syndromes (TABLE 1). Most prominent among them are HGPS which are caused by genetic defects in nuclear envelope proteins, as well as classical Werner syndrome, Cockayne syndrome, Bloom syndrome, xeroderma pigmentosum, ataxia telangiectasia, trichothiodystrophy, dyskeratosis congenita (DKC) and mosaic variegated aneuploidy syndrome, which are caused by defects in DNA repair and maintenance proteins (TABLE 1). The cellular defects that are observed in these and other human premature ageing models, including genomic and proteomic instability, altered metabolism and loss of regenerative potential, overlap with defects that occur during physiological ageing in humans. Moreover, there are

striking commonalities between organismal defects in several premature ageing diseases and age associated diseases (AADs).

However, as premature ageing syndromes only represent some aspects of the normal ageing process, it is not surprising that progeroid syndromes are typically only associated with a subset of AADs (TABLE 1). For example, HGPS involves extensive cardiovascular and osteoporotic pathology, whereas premature ageing disorders caused by mutations in DNA repair proteins are often characterized by cancer susceptibility and neurodegeneration. These parallels suggest common aetiologies between premature ageing syndromes and AADs [28].

The nuclear lamina (NL) is a meshwork of lamins and lamin-associated proteins adjoining the inner side of the nuclear envelope (Figure-2 A). In early embryonic cells, the NL mainly suppresses background transcription, whereas, in differentiated cell types, its disruption affects gene expression more severely. Normally, the NL serves as a backbone for multiple chromatin anchoring sites, thus shaping the spatial organization of chromosomes in the interphase nucleus (Figure-2 B). However, upon cell senescence, aging, or in some types of terminally differentiated cells and lamin-associated diseases, the loss of NL-chromatin tethering causes drastic alterations in chromosome architecture (Figure-2 B) [29].

In eukaryotes, the densely packed heterochromatin is mainly located at the nuclear periphery, whereas the less compact euchromatin occupies a more interior nuclear position. Heterochromatin is subdivided into densely-packed constitutive heterochromatin, covering pericentromeric and telomeric chromosomal regions, and less condensed facultative heterochromatin located in the chromosomal arms. Recent electron microscopy observations indicate that during interphase chromatin is represented by a 5- to 24-nm nucleosomal chain aggregated into irregular clusters with a higher packaging density at the nuclear periphery [30]. The nuclear lamina (NL) is a meshwork consisting of A- and B-type lamins and lamin-associated proteins which lines the inner nuclear membrane (Figure-2 A-B) [31] and participates in the compaction of peripheral chromatin. Chromosomal regions interacting with the NL, the so-called lamina-associated domains (LADs), have been identified in various organisms from nematode to human [32].

### 2.1. Therapeutic approach for aging and laminopathies

To think that treatments for premature aging diseases could contribute to increase of life in normal human belongs to theoretical speculation; for example the absence of progerin does not contribute to increase in lifespan (Figure-3 B). On the other hand, we know that loss of lamin A is not detrimental, then elimination of lamin A precursors, from diseased cells seems like a safe therapeutic strategy [17]. By using antisense oligonucleotides to knock down prelamin A, was demonstrate that reduction of prelamin A levels indeed had a positive effect and resulted in correction of morphological abnormalities of the cell nucleus in Zmpste24−/− mouse embryonic fibroblasts [33].

Similar results should also be achievable by RNA interference approaches; the use of CRISPR-mediated adenine base editor (ABE) to repair mutations of HGPS, attenuate symptoms, and extend lifespan of mice by a single injection of ABE-expressing adeno-associated virus 9 (AAV9) at postnatal mice and improved vitality and greatly extended the mice lifespan from 215 to 510 days. These findings demonstrate the potential of in vivo base editing as a possible treatment for HGPS and other genetic diseases by directly correcting their root cause [34, 35].

Thus, elimination of lamin A might be a suitable therapeutic strategy not only for HGPS, but also for other laminopathies such as some forms of muscular dystrophy, although this approach might be limited to the group of laminopathies in which mutations only affect prelamin A or lamin A, but not lamin C so that it can have a redundant effect to lamin A [33, 36, 18, 37, 38] (Figure-4).

When we turn to understanding the action of telomeres *in vivo* we verified that there are animals models for studying senescence by telomeres [39] since animals that live longer with a more active telomerase [40].

However, the role of telomerase in organismal aging has remained unaddressed, in part because of the cancer-promoting activity of telomerase [40]. So, to circumvent this problem, expression of gene telomerase reverse transcriptase (TERT), was induced in mice engineered to be cancer resistant by means of enhanced expression of the tumor suppressors p53, p16, and p19ARF. In this context, TERT overexpression delay in aging in mice by extension of the median life span. Thus the constitutive expression of TERT provides antiaging activity in the context of a mammalian organism[40].

The above-mentioned transgenic mice, called super-p53 (Sp53) or super-p16/Arf (Sp16/SArf), possess three gene doses of each of the indicated tumor suppressors instead of the normal diploid gene dose; this increase in tumor

suppression activity is sufficient to significantly increase cancer resistance [41, 42]. The single transgenic Sp53 or Sp16/SArf mice have a normal aging and life span [41,42], but the combination of both transgenes in doubly transgenic Sp53/Sp16/SArf mice results in delayed aging, probably because of the ability of these tumor suppressors to eliminate cellular damage and damaged cells [43]. Here, we address the role of telomerase in mouse fitness and aging by generating TERT-transgenic mice in a tumor-resistant genetic background, in an effort to dissociate the effects of telomerase on cancer and aging. In this context, was demonstrate that TERT overexpression has antiaging activity.

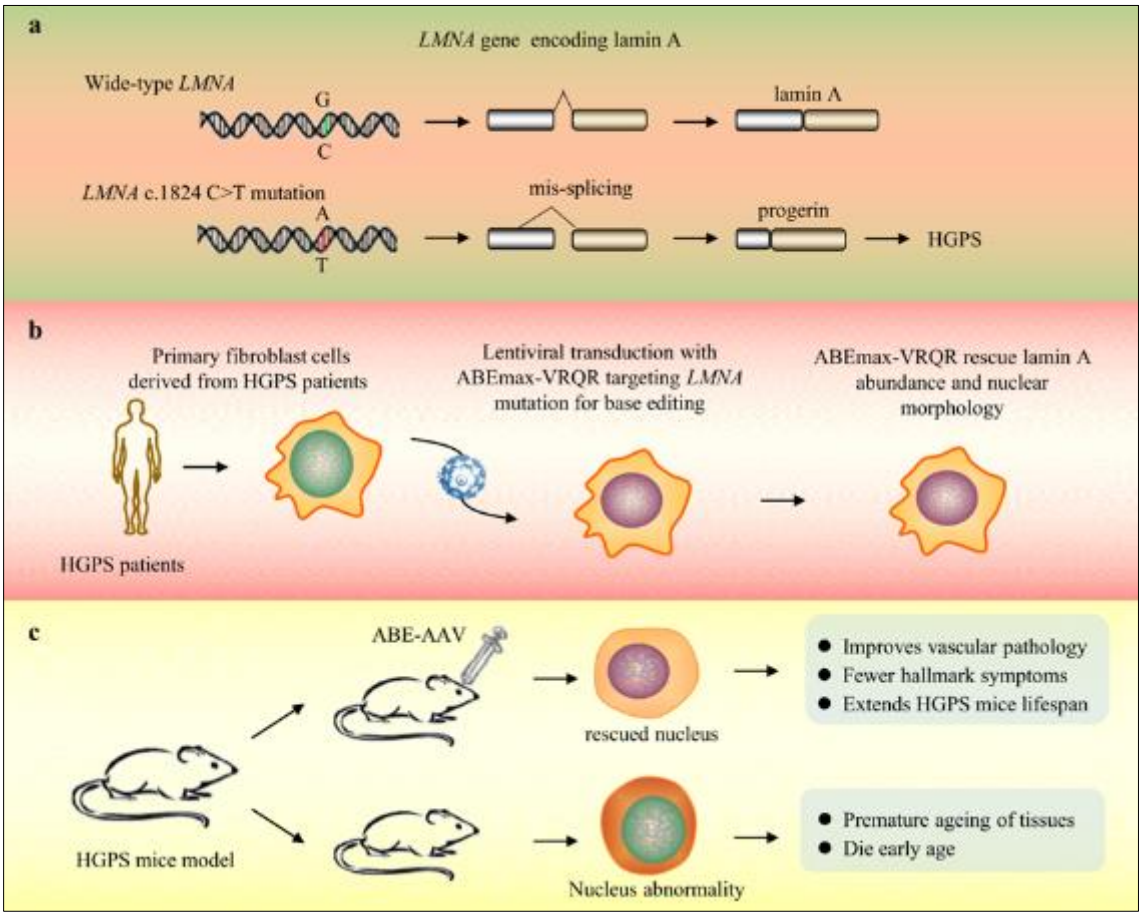


**Figure 4** Programmable base editing rescues Hutchinson–Gilford progeria syndrome. (a) A single base mutation at 1824 locus in LMNA gene results in mis-splicing and subsequently translates into a truncated lamin A protein, termed progerin, which causes Hutchinson–Gilford progeria syndrome (HGPS). (b) ABEmax-VRQR corrected human LMNA mutation in two primary fibroblast cells derived from HGPS patients. Using the lentiviral delivery delivered ABEmax-VRQR and sgRNA targeting LMNA c.1824 C > T mutation, resulting in gene editing of the LMNA loci and subsequently rescuing lamin A abundance and nuclear morphology. (c) ABEmax-VRQR treatment in HGPS mice model. Koblan et al. used the clinical adeno-associated virus vector for co-packaged ABEmax-VRQR to make the correction of mutation in many tissues, but not all, in mouse model, resulting in improved vascular pathology and extended the HGPS mice lifespan. Courtesy of (Lin *et al*., 2021) by Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

So, the mice that constitutively express the telomerase TERT gene in the stem and proliferative compartments of a wide range of epithelial tissues (was, hereafter as K5-TERT and TgTERT mice) [44, 45] and crossed with cancer-resistant Sp53 and Sp16/SArf mice [41,42,46] resulting in the TERT-transgenic mice with increased tumor resistance named Sp53/Sp16/SArf/TgTERT mice. So TgTERT tissues show ≤10-fold increase in telomerase activity compared to wild-type tissues [44, 45], which is within the range of telomerase activation upon various stimuli, such as T cell activation[47,48]. TgTERT-associated phenotypes include increased wound healing, improved epidermal stem cell mobilization/proliferation, and increased tumorigenesis [44,45,48,49}. These effects of TERT overexpression are noticeable already at young ages and require the telomerase RNA component (TERC) [48,49,50], thus suggesting that they are the consequence of increased telomerase activity and longer telomeres in these mice. Nevertheless, it is relevant to note that other authors have suggested additional roles of TERT overexpression on stem cell proliferation, which are independent of telomerase activity [51] and could also have a positive impact on aging and longevity. Thus

whas used a single set of parental mice (TgTERT × Sp53/Sp16/SArf) to obtain two pairs of cancer-resistant strains namely, Sp53 and Sp53/TgTERT strains, and Sp53/Sp16/SArf and Sp53/Sp16/SArf/TgTERT strains. To analyze if the tumorigenic effects of the TERT transgene was canceled in the Sp53 and Sp53/Sp16/SArf backgrounds. Importantly, both the incidence and time of development of malignant tumors (lymphomas, sarcomas, and carcinomas) did not differ significantly between Sp53and Sp53/TgTERT cohorts, or between Sp53/Sp16/SArf and Sp53/Sp16/SArf/TgTERTmice, thus indicating that the tumorigenic effects of TgTERT have been effectively canceled in these backgrounds[40].

Alternatively, telomerase-deficient mice have served as a model system to study the adverse cellular and organismal consequences of wide-spread endogenous DNA damage signalling activation *in vivo*. Telomere loss and uncapping provokes progressive tissue atrophy, stem cell depletion, organ system failure and impaired tissue injury responses. Another work sought to determine whether entrenched multi-system degeneration in adult mice with severe telomere dysfunction can be halted or possibly reversed by reactivation of endogenous telomerase activity. To this end, was engineered a knock-in allele encoding a 4-hydroxytamoxifen (4-OHT)-inducible telomerase reverse transcriptase-oestrogen receptor (TERT-ER) under transcriptional control of the endogenous TERT promoter. Homozygous TERT-ER mice have short dysfunctional telomeres and sustain increased DNA damage signalling and classical degenerative phenotypes upon successive generational matings and advancing age. Telomerase reactivation in such late generation TERT-ER mice extends telomeres, reduces DNA damage signalling and associated cellular checkpoint responses, allows resumption of proliferation in quiescent cultures, and eliminates degenerative phenotypes across multiple organs including testes, spleens and intestines [39].

However, was investigated if senescent cells are causally implicated in age-related dysfunction and whether their removal is beneficial. To address these fundamental questions, was use of a biomarker for senescence, p16(Ink4a), to design a novel transgene, INK-ATTAC, for inducible elimination of p16(Ink4a)-positive senescent cells upon administration of a drug. Here was show that in the BubR1 progeroid mouse background, INK-ATTAC removes p16(Ink4a)-positive senescent cells upon drug treatment. Thus, in tissues such as adipose, skeletal muscle and eye in which p16(Ink4a) contributes to the acquisition of age-related pathologies, the removal of p16(Ink4a)-expressing cells delayed onset of these phenotypes. Furthermore, late-life clearance attenuated progression of already established age-related disorders. These data indicate that cellular senescence is causally implicated in generating age-related phenotypes and that removal of senescent cells can prevent or delay tissue dysfunction and extend health span [52].

**Figure 5** Gordon LB, Brown WT, Collins FS. Hutchinson-Gilford Progeria Syndrome. 2003 Dec 12 [Updated 2019 Jan 17]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Figure 1. [Female age 11 years and male age six years with HGPS displaying classic features]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1121/figure/hgps.F1/

## 3. Conclusion

when we think in natural aging processes and models that theoretically mimic one age-related factor (TABLE 1), we cannot extend much further than the field of biological speculation just children who suffer from the HGPS syndrome, for example, are children and not old people because they do not undergo an accelerated development, but rather have a genetic defect that does not even phenotypically resemble natural old age, see (Figure-5).

In the same way it seems that genetic problems only cause morbidities and the increase of one or another gene also causes problems such as TERT for example and the elimination of truncated progerin does not cause an increase in the animals' lifespan.

However, it also seems possible to increase the lifespan of animals by increasing certain genes such as Sp53/Sp16/SArf/TgTERT so the extent to which a series of genes and tissue-specific fine regulations could increase a mammal's lifespan to the point of rendering it immortal may be true or speculation.

Thus, we also have to consider the fact that each tissue type has a totally different epigenetic pattern and mitosis rates, so there may be an as yet unknown link between the number of mitoses and mitochondrial aging. So, it may be that a treatment for mitochondrial aging is its restitution using a primitive mitochondrial-like strain of primordial mitochondria with todipotent restorative capabilities of both the mitochondrial of non-mitotic cells as well as the organelles of mitotic tissues.

Finally, to conclude, we are still a long way from fully elucidating the aging process, it could also be that a drug, biogenic or phytotherapeutic, discovered by chance, could be a solution to significantly extend human lifespan.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors declare that there is no conflict of interest. We authorize the full disclosure of the manuscript text and data.

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