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Perspective

Programmed Aging Theory Defeats Damage Accumulation Theory of Aging

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Abstract: There are two major categories of aging theories: programmed aging theory and damage accumulation theory. The damage accumulation theory currently prevails in mainstream research, given that accumulated damage of diverse molecules has been observed in senescent cells. Nevertheless, observable phenomena do not necessarily correspond to the fundamental truth. Over billions of years of evolution, life has evolved complete coping mechanisms to eliminate various forms of molecular damage, which means aging cannot stem from damage accumulation. For example, senescent hematopoietic stem cells display 1500 significantly upregulated genes and another 1500 downregulated genes. This evidence proves that aging is essentially a programmed biological process. Genes with upregulated expression are predominantly enriched in stress response and inflammatory pathways, whereas downregulated genes are largely related to chromatin remodeling and DNA repair. This reveals that molecular damage accumulation is pre-programmed by intrinsic biological routines, rather than an insurmountable defect for living organisms. The Telomere DNA and ribosomal DNA co-regulation model for cell senescence (TRCS) proposes that organismal development, maturation and aging is a genetic program driven by telomeres and/or rDNA via the p53 pathway.

Keywords: programmed aging theory; damage accumulation theory of aging; cellular senescence; telomeres; 45S rDNA; p53

1. Introduction

We all age gradually and eventually die, and many diseases are caused by aging. Therefore, understanding the mechanisms of aging is critically important. Although more than 300 theories of aging have been proposed [1], they all suffer from limitations and appear to have reached a dead end, resulting in stagnant progress in lifespan intervention. According to the annual analysis of lifespan-extending drugs/compounds in DrugAge, despite the continuous growth of related research in recent years, no significantly greater lifespan-extending effects have been observed [2]. Even many anti-aging drugs claimed to prolong lifespan have failed the rigorous Interventions Testing Program (ITP) conducted by the National Institute on Aging (NIA) of the United States. For example, NR, an anti-aging compound that boosts NAD^+ levels, was found to shorten the lifespan of male mice by 3% [3]. Thus, an anti-aging drug that cannot extend lifespan should not be labeled as such; at best, it can only be classified as a dietary supplement.

Theories of aging fall into two categories: programmed aging theories and damage accumulation theories. Programmed aging theories posit that organismal development, maturation, and aging are all controlled by a biological program. Damage accumulation theories propose that aging arises from the gradual buildup of random molecular and cellular damage, which cannot be fully counteracted by repair systems. This framework includes damage to nuclear DNA and mitochondrial DNA (mtDNA), protein misfolding or cross-linking, and the accumulation of various metabolic wastes. Gyenis et al. argued that DNA damage may be the primary cause of

cellular senescence [4]. Sinclair et al. [5] proposed the Information Theory of Aging (ITOA), which states that DNA damage and repair processes lead to the loss of epigenetic information, thereby causing cellular senescence. The ITOA therefore falls under the category of damage accumulation theories of aging. Meyer et al. argued [6] that aging after sexual maturity is no longer governed by a program; aging clocks such as DNA methylation do not imply an intrinsic program, but instead reflect the stochastic accumulation of molecular errors and damage. Thus, both Gyenis et al. and Meyer et al. support the damage accumulation theory of aging.

2. The Damage Accumulation Theory of Aging Is Invalid

A valid theory cannot tolerate any counterevidence; the more counterevidence there is, the less credible the theory becomes. Since the damage accumulation theory of aging contains numerous flaws and even yields contradictory intervention outcomes, this theory is incorrect.

2.1. Evidence that Damage Accumulation Does Not Cause Cellular Senescence

DNA damage is thought to be a major cause of cellular senescence [4,5]. However, ionizing radiation greatly increases damage to nuclear DNA and mtDNA, yet sublethal doses of ionizing radiation have been shown to extend lifespan in Drosophila, houseflies, rats, and mice [7–10]. In Japan, atomic bomb survivors have been found to live longer and have a lower cancer incidence than the general population [11]. It is commonly believed that stronger DNA repair capacity correlates with longer lifespan. Nevertheless, cockroaches and tardigrades possess extremely strong DNA repair abilities, yet under favorable conditions, their lifespans are only a few months.

The number of mutations present in aging yeast cells is considerably low. Some genetically modified mouse strains with high levels of free radicals or elevated mutation rates do not exhibit premature aging and have no shorter lifespan than wild-type mice. Cardiomyocyte nuclei in aging mice harbor only a small number of nuclear DNA mutations [12]. Although the accumulation of nuclear DNA mutations increases cancer risk, it does not accelerate aging [13]. The nuclei of HeLa cells rapidly accumulate DNA damage [14]; nevertheless, HeLa cells maintain unlimited division potential. In successive recloning of mice, in the absence of the natural reproductive elimination mechanism that weeds out the weak and preserves the strong—the marathon race of sperm in the oviduct—DNA accumulates an increasing number of mutations. From the 1st to the 57th generation, approximately 69 single-nucleotide mutations and 1.4 small insertions/deletions occur per generation on average. More critically, large-scale chromosomal structural aberrations emerge, such as complete loss of the X chromosome, large chromosomal deletions, or translocations. These accumulated mutations lead to a gradual decline in the success rate of mouse cloning. All the phantom mice of the 58th generation died within 24 h after birth. However, the average lifespan of mice from both the 1st and 57th generations was two years, indicating that DNA damage and accumulation do not cause aging [15]. Collectively, these lines of evidence demonstrate that DNA mutation and accumulation are not the cause of cellular and organismal aging.

In plants, planarians, and *Turritopsis dohrnii* (immortal jellyfish), which lack an adaptive immune system and can reproduce asexually, cells with nuclear DNA mutations cannot be selectively eliminated, yet this does not impair their asexual reproduction or immortality. New plant varieties can be bred using cuttings, which relies on genetic mutations in stem cells of the meristem. However, the epigenetics of plant stem cells does not undergo senescence [16]. More than 70% of iPSCs exhibit detectable DNA damage [17], yet the epigenetics of iPSCs also does not senesce [18]. Therefore, the accumulation of DNA damage does not cause cellular senescence.

Oxygen free radicals can cause DNA mutations, protein cross-linking and denaturation. However, deletion of the mitochondrial superoxide dismutase gene sod-2 extends the lifespan of *Caenorhabditis elegans*, despite a significant increase in oxidatively damaged proteins [19]. Heterozygous mutation of mitochondrial superoxide dismutase (SOD2) in mice leads to increased oxidative damage and mutated mtDNA, but does not shorten lifespan [20]. Accumulation of mtDNA mutations in mice does not accelerate aging or shorten lifespan [21,22]. Analysis of age-related changes in mtDNA mutations in human blood reveals that these mutations only accumulate substantially after the age of 60, whereas senescence initiates far earlier. Such observations fail to support the hypothesis that mtDNA mutations act as a driver of aging [23]. Treatment of nematodes with paraquat, a herbicide that generates superoxide and hydrogen peroxide, can extend nematode lifespan by up to 58%. This lifespan-extending effect of paraquat was abolished by subsequent treatment with the antioxidant N-acetylcysteine [24]. Methylene blue (MB) is a potent antioxidant that can penetrate organelles such as lysosomes and mitochondria. However, ITP testing showed that it did not extend the mean lifespan of mice [25]. α-Lipoic acid is an antioxidant effective in preventing lipid peroxidation and the accumulation of its harmful byproducts, including toxic aldehydes such as acrolein. However, α-lipoic acid significantly shortened the median lifespan of mice [26]. Therefore, although antioxidants reduce

various forms of damage, they fail to extend animal lifespan. This evidence alone is sufficient to refute the theory that aging is caused by the accumulation of various random damages.

Geranylgeranylacetone (GGA) induces the expression of heat shock proteins in mammalian tissues, ensuring proper protein folding. However, ITP testing showed that GGA did not extend lifespan in mice [3]. Therefore, oxidative damage and misfolding of proteins, as well as DNA mutations, cannot be the causes of cellular senescence.

Damaged waste materials such as dysfunctional mitochondria and proteins can be degraded through the autophagy pathway. Resveratrol and curcumin are able to enhance autophagy; however, ITP testing has shown that they fail to extend lifespan in mice [27]. Moreover, resveratrol has been found to accelerate neuronal aging and induce brain atrophy in lemurs [28,29]. Ovarian aging in mice is associated with elevated autophagy in granulosa cells [30]. Chloroquine (CQ) is the only autophagy inhibitor approved by the Food and Drug Administration (FDA) [31]. Nevertheless, CQ has been shown to increase the maximum lifespan of rats by 13%, an effect comparable to some of the most potent anti-aging compounds ever tested in mouse models [32]. Suppressing autophagy in aged *Caenorhabditis elegans* can instead extend lifespan by up to 50% [33], while increasing intestinal autophagy in *C. elegans* actually accelerates aging [34]. These findings indicate that damage accumulation does not drive cellular aging as commonly assumed, and excessive enhancement of autophagy may instead promote aging.

2.2. Damage Accumulation Can Be Overcome

The damage accumulation theory of aging fails to explain the enormous differences in lifespan between Caenorhabditis elegans, which lives only about ten days, Arctic clams and Greenland sharks that live 400 to 500 years, leukocytes in the human body that survive only a few days, neurons and cardiomyocytes that live for decades, as well as annual plants and plants that live for thousands of years, which suggests that damage can be completely counteracted by repair systems.

Aged somatic cells can be induced into young iPSCs, and organisms can remain free of damage accumulation during the growth and developmental period. The lifespan of post-mitotic human neurons and cardiomyocytes is almost as long as that of the individual, indicating that damage can also be overcome. For example, mutated mtDNA can be eliminated via mitophagy and mitocytosis [35,36]. At the individual level, mutated nuclear DNA can be (1) repaired; (2) if repair fails, apoptosis will be initiated; (3) if it is neither repaired nor undergoes apoptosis, it will eventually be monitored and eliminated by the immune system. Therefore, the gradual accumulation of cells with DNA mutations with age is caused by the aging of the immune system.

Lipofuscin (LF) is the main component of senile plaques. In 1973, Tappel et al. added vitamin E to the diet and fed adult rats for one year. They found that neuronal LF was indeed reduced, but there was no decrease in mortality [37]. Squirrel monkeys (*Saimiri sciureus*) fed a diet containing 2% protein for 9–15 weeks developed abundant LF in the nervous system, and subsequent feeding with a diet containing 25% protein reduced LF accumulation [38]. However, a high-protein diet accelerates aging and shortens lifespan [39]. Therefore, the accumulation of LF is only a consequence of cellular senescence rather than a cause, and the repair system is capable of clearing accumulated LF.

In 1958, Yoshida reported [40] that within 8 h, chloroplasts in nucleated protoplasts of *Elodea densa* underwent senescence and structural disruption, whereas chloroplasts in enucleated protoplasts remained green and continued to accumulate starch. In 1975, Wright and Hayflick transplanted a young nucleus into enucleated senescent cytoplasm. As a result, the cells resumed division and continued to divide for the remaining number of divisions characteristic of young cells, indicating that the determinant of cellular senescence is the cell nucleus [41], rather than organelles in the cytoplasm such as mitochondria. In other words, as long as the nucleus remains young, lipofuscin (LF), mutated mtDNA, misfolded, cross-linked and denatured proteins in the cytoplasm will not accumulate to harmful levels.

In summary, the damage accumulation theory of cellular senescence is invalid.

3. Aging Is Programmed

Whether the aging process is controlled by a program or results from the accumulation of random damage is a fiercely debated issue between two schools of thought in aging research. Much evidence has been presented above to show that the damage accumulation theory of aging is invalid. Since each species has a relatively fixed timetable for growth, development, maturation, aging, and death, this represents a kind of program, and further evidence also indicates that the essence of aging is a program.

3.1. Programmed Gene Expression Indicates That Aging Is Programmed

The processes of development, maturation, and aging in an individual are also accompanied by gradual changes in the gene expression profile. Both Gyenis et al. and the ITOA proposed [4,5] that DNA damage may underlie changes in the gene expression profile. However, the alterations in gene expression and DNA methylation profiles during development, maturation, and aging are highly ordered [42], suggesting that aging cannot result from the accumulation of random DNA damage. During mouse aging, plasma proteins that increase are mostly detrimental to health, whereas those that decrease are mainly beneficial [43]. Since random damage is non-directional, how could plasma protein composition undergo such regular changes? This further supports that aging is a genetic program.

If the programmed theory of aging is correct, cellular aging must involve the timed, programmed expression of gene groups along the chromosome. This is indeed the case. For example, fetal liver cells primarily express α-fetoprotein, postnatal liver cells express albumin, and in old age, the albumin gene is gradually silenced while other genes are activated [44–46]. Because albumin is indispensable, measuring albumin levels can predict an individual's lifespan [47,48].

Starting from a fertilized egg, the gene expression profile of a life form can be broadly divided into three phases: early, middle, and late. The early gene expression profile is mainly associated with embryonic development; the middle profile focuses primarily on maintaining health and reproductive function; and the late profile is predominantly linked to the disruption of normal physiological functions. Accordingly, the processes of development, maturation, aging, and the onset of age-related diseases represent a gradual shift from physiologically beneficial gene expression patterns toward detrimental ones [49]. The late-stage gene expression profile underlies the pathogenesis of degenerative disorders such as arteriosclerosis, atherosclerosis, hypertension, and Alzheimer's disease (AD). For instance, young macrophages mainly express VEGF-A165A, an isoform of vascular endothelial growth factor A that promotes angiogenesis and enhances tissue repair. In contrast, senescent macrophages predominantly produce VEGF-A165B, an alternative isoform that inhibits angiogenesis and impairs tissue regeneration [50]. It has long been assumed that low-density lipoprotein cholesterol (LDL-C) infiltrates the vascular wall only after structural damage creates an opportunity for deposition. However, research reveals that SR-B1, a receptor capable of actively uptaking circulating LDL-C, is upregulated in aged vascular endothelial cells, thereby increasing LDL-C internalization [51]. Meanwhile, senescent macrophages exhibit reduced expression of the transcription factor TFEB, which elevates levels of p62—a protein that suppresses lysosomal lipid degradation within macrophages [52]. Consequently, aged endothelial cells actively enhance LDL-C uptake while senescent macrophages diminish lipid clearance, tipping the balance toward lipid accumulation and plaque progression. Arteriosclerosis and plaque formation are major contributors to hypertension and cardiovascular and cerebrovascular diseases. Clusterin (Clu) is upregulated in aged hematopoietic stem cells, promoting myeloid differentiation and increasing the production of myeloid cells [53]. In Alzheimer's disease, methylation within the promoter region of the amyloid-β precursor protein (APP) decreases with age, leading to enhanced APP expression [54]. Concurrently, expression of low-density lipoprotein receptor-related protein 1 (LRP1)—which transports amyloid-β (Aβ) across the blood-brain barrier into peripheral circulation—is downregulated with advancing age [55]. This dual mechanism increases Aβ production while impairing its clearance, gradually driving the emergence of AD pathological features and clinical symptoms.

Although DNA damage occurs randomly, the efficiency of DNA repair is determined by biological programming. For example, during the aging of hematopoietic stem cells, approximately 1500 genes undergo either upregulation or downregulation. Specifically, stress-response and inflammatory genes detrimental to health are upregulated with advancing age, while chromatin remodeling and DNA repair genes beneficial to health are downregulated [56], thereby increasing inflammation and the rate of DNA mutation.

Telomere length is negatively correlated with the expression of the *DUX4* gene [57]. DUX4 is negatively correlated with *MHC-I* gene expression; therefore, as telomeres continue to shorten, DUX4 expression is gradually upregulated and MHC-I expression is gradually downregulated, so that upregulation of DUX4 impairs antigen presentation by MHC [58], which compromises the clearance of mutated cells by the immune system, leading to greater accumulation of DNA mutations and a higher incidence of tumors in aging individuals. This indicates that the rapid accumulation of various types of damage in aging individuals and the outbreak of tumors at specific ages are also pre-set by a program.

Since DNA mutation burden in somatic cells is positively correlated with age, many people intuitively believe that DNA mutations cause aging. However, the DNA mutation rate is the same in non-dividing and frequently dividing cells [59]; regardless of lifespan, animals that age faster accumulate more mutations per year, but the mutation rates are similar once they reach senescence [60]; although smoking increases the DNA mutation rate,

the mutation level does not rise significantly beyond 23 packs per year [61]; the more gene mutations present in a tumor cell, the more likely immunotherapy is to be effective [62]; bone marrow stem cells with the same oncogenic mutations proliferate in aged mice but not in young mice [63]. These lines of evidence also indicate that age-related DNA mutation burden is likewise predetermined by a program, or is negatively correlated with the sensitivity of immune surveillance.

Although global genomic DNA methylation levels gradually decrease with age, some genes such as *IFNγ*, *F3*, *CRAT*, and *OGG* become more methylated during aging, whereas *GCR*, *iNOS*, and *TLR2* become more demethylated [64]. Up to 90% of age-related changes in the epigenome are deterministic [65], indicating that epigenetic changes with age follow a regular pattern. Aging is therefore unlikely to result from the accumulation of random damage but is instead programmed. Furthermore, the rate of individual aging is nonlinear [66], which is also difficult to explain by damage accumulation. Thus, aging is controlled by a program.

Accordingly, the conventional anti-aging strategy is to inhibit certain upregulated genes and activate or overexpress certain downregulated genes. However, such interventions at the metabolic and signaling pathway levels only extend lifespan modestly and have significant side effects; furthermore, they cannot achieve rejuvenation. This explains why, despite the continuous discovery of more anti-aging drugs/compounds in recent years, none have shown a more significant lifespan-extending effect [2].

In summary, to identify the root cause of aging, we should not look for which genes are upregulated or downregulated with age, but rather why these genes are upregulated or downregulated with age.

3.2. Aging after Sexual Maturity Is Still Programmed

Whether the aging process is controlled by a program or results from the accumulation of random damage is a fiercely debated issue between two schools of thought in aging research. Both sides agree that the rate of growth and development and the timing of sexual maturity are controlled by a program. However, after sexual maturity, opponents of programmed aging argue that aging has a negative effect on the individual. Since natural selection acts only on individuals, it is impossible for individuals to evolve and maintain a program that is detrimental to themselves, and aging can only be the result of the gradual accumulation of randomly occurring damage to the body.

Through long-term evolution, organisms have developed redundant repair systems to overcome various types of damage. Therefore, even after sexual maturity, aging cannot result from the gradual accumulation of random damage. The short-lived African killifish (and other species) can illustrate that aging after sexual maturity is still programmed [67]. The eggs of killifish enter diapause during the dry season and hatch again when ponds form in the rainy season. In Zimbabwe, where the rainy season is very short and ponds dry up rapidly afterward, the local strain *Nothobranchius furzeri* has a lifespan of only 3 months, matching the length of the rainy season. In Mozambique, where the rainy season is four times longer, the strain *Nothobranchius rachovii* can live for 9 months. In Tanzania, the strain *Nothobranchius guentheri* lives in a region with two rainy seasons and has a lifespan of up to 16 months. When these three killifish species are reared under identical laboratory conditions, the differences in their lifespans persist [68]. This demonstrates that aging is programmed, because the accumulation of random damage cannot explain why such closely related killifish species with nearly identical body structures show such large lifespan differences that precisely correspond to the duration of the rainy season in their native habitats [69].

4. The Operating Mechanism of the Program Controlling Development and Aging

During a life cycle, the sequence and copy number of most genes on chromosomes are fixed. Therefore, to enable timed, programmed expression of these constant genes along the temporal axis, a countdown substance (equivalent to the sand in an hourglass timer, Figure 1) is required to drive the process. Since some individuals can live for more than a century—for example, the Greenland shark can live up to 400 years—the countdown substance that drives the genetic program must be extremely stable and have no half-life. However, proteins, RNA, mtDNA, as well as chemical modifications of nuclear DNA and histones are all unstable, possess a half-life, and are in a dynamic equilibrium of continuous degradation and renewal. For instance, DNA methylation and demethylation, as well as histone acetylation and deacetylation, occur simultaneously. Thus, they cannot establish a temporal measure and lack the properties of a timing substance. In other words, the root cause of aging does not lie in RNA, proteins, mtDNA, or various epigenetic modifications.

Figure 1. The sand in the hourglass corresponds to the "countdown substance". Photo by Andrej Lišakov on Unsplash.

Telomeres are composed of multiple copies of tandemly repeated DNA arrays, making them ideal candidates for countdown substances. Moreover, increasing telomere length can significantly boost the number of cell divisions and reduce aging markers [70,71], an effect that cannot be achieved by other anti-aging interventions, indicating that telomere shortening is one of the root causes of cellular senescence. However, telomeres do not shorten with age in many species or in certain cell types within the same species, and maintaining telomere length fails to immortalize cells. Therefore, a second set of countdown substances exists in the nucleus.

Since ribosomal DNA (rDNA) also exists as multi-copy tandem repeat arrays, it becomes the optimal candidate for a second countdown mechanism within the nucleus. Accordingly, I proposed the Telomere DNA and Ribosomal DNA Co-Regulation Model for Cell Senescence (TRCS). The TRCS model holds that the nucleus contains two sets of countdown substances, analogous to a double mainspring clock (Figure 2). Shortening of telomere arrays and/or rDNA arrays elevates the level of the tumor suppressor protein p53, thereby triggering cellular senescence (Figure 3) [72].

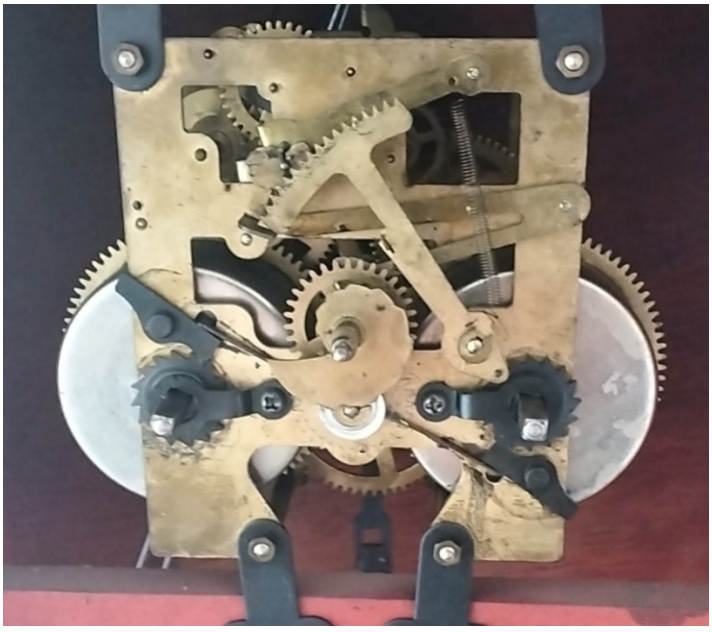

Figure 2. A double mainspring clock as an analogy for the dual-countdown mechanism proposed in the TRCS model. Photo by the author.

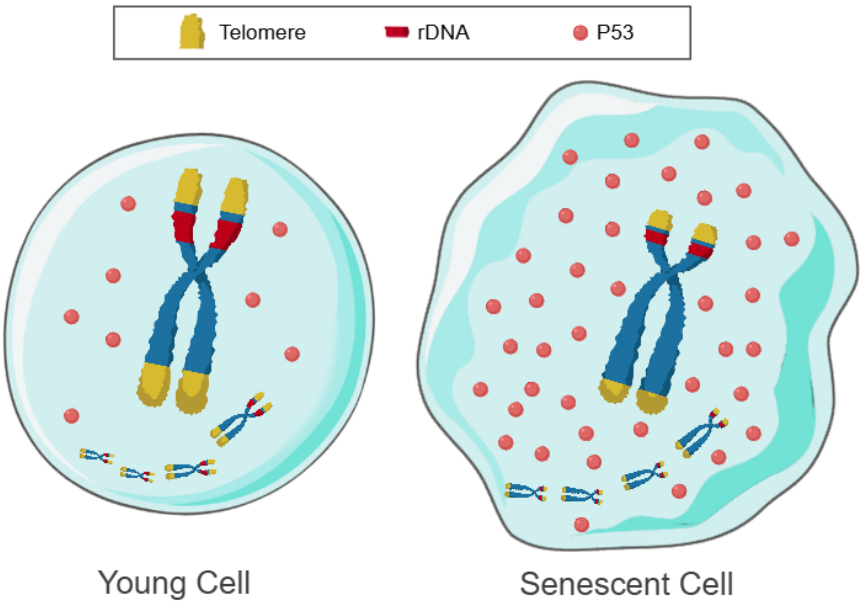

Figure 3. Telomere DNA and ribosomal DNA co-regulation model for cell senescence. Left: Long telomere and rDNA arrays: rapid degradation of p53, youthful cells. Right: Short telomere and rDNA arrays: slow degradation of p53, cellular senescence. This figure is reproduced from Huang and Hu of Ref. [69] under the terms of the Creative Commons Attribution (CC BY) license.

Approximately 1/10 of human gene promoters contain p53-binding sites and can therefore be classified as p53-responsive genes [73]. p53 not only downregulates the overall rate of protein synthesis but also acts as a transcription factor that simultaneously represses and activates numerous genes. Thus, as telomere and/or rDNA arrays gradually shorten with age, p53 forms a concentration gradient along the temporal axis. By binding to promoters and enhancers of various genes, p53 upregulates some genes and downregulates others, thereby driving the programmed expression of gene clusters on chromosomes along the time axis [74]. Since differentiated cells of different types harbor distinct genetic programs, they exhibit different gene expression patterns during aging.

Notably, recent research by Ziyu Lu, Wei Zhou, and colleagues investigated how cellular composition and gene regulation undergo systematic temporal changes during mammalian aging. Their findings demonstrate that aging is not random degeneration, but a genetic program driven by specific molecular mechanisms [75]. In *Arabidopsis thaliana*, aging follows a similar pattern to that observed in mammals, with DNA methylation levels gradually declining with age. However, mutations in the *tcx5/6* genes maintain stable DNA methylation throughout the lifespan, while the aging rate remains comparable to that of wild-type plants [16]. During aging, most somatic cells exhibit global DNA hypomethylation, whereas aging hematopoietic stem cells are characterized by global hypermethylation [76]. Deletion of the *GADD45B* gene also elevates DNA methylation in young hematopoietic stem cells, producing epigenetic profiles similar to those of aged hematopoietic stem cells. Nevertheless, such methylation alterations do not impair stem cell function; self-renewal and differentiation capacities remain intact [77]. Collectively, these lines of evidence indicate that the loss of epigenetic information is more likely a consequence, rather than a driving cause, of aging, thereby invalidating the ITOA. The programmed temporal expression of genes underlying individual development, maturation, and aging is presumably governed by molecular clocks such as telomeres and/or rDNA, rather than by epigenetic regulation.

5. Evidence for the TRCS Model

The validity of a theory depends on its self-consistency. Since the shortening of telomere DNA and rDNA arrays is the root cause of cellular senescence and acts as the countdown substance driving the programmed expression of gene clusters, the telomere DNA and rDNA lost in somatic cells must be replenished in germ cells or early embryonic cells; otherwise, life cannot be passed on through generations. Fortunately, evidence has shown that telomere DNA and rDNA lost in somatic cells can be replenished in early embryonic cells or germ cells [78–80]. In mouse hematopoietic stem cells, activation of mTOR1 leads to shortening of rDNA arrays [81], whereas the anti-aging drug rapamycin can inhibit rDNA transcription and cell replication by suppressing mTOR1, thereby slowing replicative senescence and extending lifespan in mice. Accordingly, from first principles, the lifespan of a species is determined by the shortening rate of telomere DNA arrays and/or rDNA arrays.

The TRCS model previously proposed that shortening of telomere and/or rDNA arrays leads to elevated levels of the tumor suppressor protein p53, driving cells into a senescent state. The rejuvenation mechanism underlying pluripotent reprogramming was attributed to the substantial lengthening of telomere and rDNA arrays [72]. Accordingly, knockdown of 45S rDNA copy number in primary mouse and human cells resulted in the expected significant upregulation of senescence markers p53, p21, p16, and SA-β-GAL, as well as marked reductions in telomere length, cell viability, and population doublings. In addition, senescent mouse cells, hESCs, and hiPSCs were examined. Telomere length and 45S rDNA copy number were significantly decreased in senescent cells, but significantly increased in hESCs and hiPSCs. These data strongly support that the rejuvenation mechanism of hESCs and hiPSCs is not due to epigenetic reprogramming, but rather to the marked increase in the length of both telomere DNA arrays and 45S rDNA arrays. Cellular senescence and the Hayflick limit are jointly regulated by telomeres and 45S rDNA, with rDNA contributing more heavily to senescence than telomeres (based on unpublished observations, with further work underway).

6. Telomeres and rDNA Are Highly Fragile Tandem Repeats

Both Gyenis et al. and the ITOA have proposed [4,5] that DNA damage may account for the changes in gene expression profiles, because the gene expression pattern in cells exposed to DNA-damaging agents closely resembles that during normal aging. Progeroid syndromes such as Cockayne syndrome are also characterized by DNA damage. This raises the question: why do DNA repair defects lead to accelerated aging?

According to the TRCS model [72], the severity of DNA damage and/or the efficiency of DNA repair mechanisms can accelerate cellular senescence through two pathways, rather than DNA damage itself causing senescence:

(1) Telomeric DNA and rDNA are multicopy tandem repetitive DNA with inherently low stability, and they are more prone to copy number loss under DNA-damaging agents, thereby accelerating replicative senescence. Furthermore, rapid telomere shortening has been observed in progeroid syndromes.

(2) Cells with DNA damage readily undergo apoptosis or are eliminated by the immune system, which stimulates surrounding cells to divide and compensate, thus accelerating replicative senescence.

Although Section 3.1 above states that "the rapid accumulation of various forms of damage in aging individuals is also genetically programmed", telomere and rDNA arrays are inherently unstable. Consequently, their shortening rates are influenced by multiple factors such as diet, physical activity, and temperature, which in turn modulate the progression of the aging program. This explains why species with longer lifespans exhibit greater lifespan variability among individuals. It also accounts for why even human identical twins can ultimately have substantial differences in longevity.

7. Organismal Aging Is Caused by Replicative Senescence of Adult Stem Cells

Extracellular matrix and intracellular cross-linked, denatured or misfolded proteins can be degraded and renewed. The reason such waste accumulates in aging tissues is that the genetic program has turned off these degradation and renewal mechanisms. Therefore, individual aging cannot be caused by the accumulation of macromolecular waste [69].

Resident stem cells have been found in all organs and tissues except the heart. Through self-renewal and cell differentiation, these stem cells continuously generate new stem cells and functional cells (terminally differentiated cells), maintaining tissue and organ homeostasis and repair. However, both stem cells and functional cells can be eliminated by the immune system due to cellular senescence, gene mutation, viral infection, and other factors. To replenish these lost cells, stem cells undergo repeated mitosis. Since adult stem cells have a limited number of divisions, and each division makes them slightly older than the previous generation, replicative senescence arises. Furthermore, functional cells differentiated from aged adult stem cells are also functionally senescent, leading to tissue, organ, and organismal aging. Therefore, the root cause of organismal aging is ultimately attributable to the replicative senescence of adult stem cells themselves [82] (Figure 4).

If adult stem cells did not undergo replicative senescence, then the loss of adult stem cells and functional cells caused by cellular senescence induced by DNA damage, cytotoxic compounds, oncogene activation, and other factors could be replenished by adult stem cells through self-renewal and differentiation. In other words, if adult stem cells did not undergo replicative senescence, individuals would remain eternally young [69].

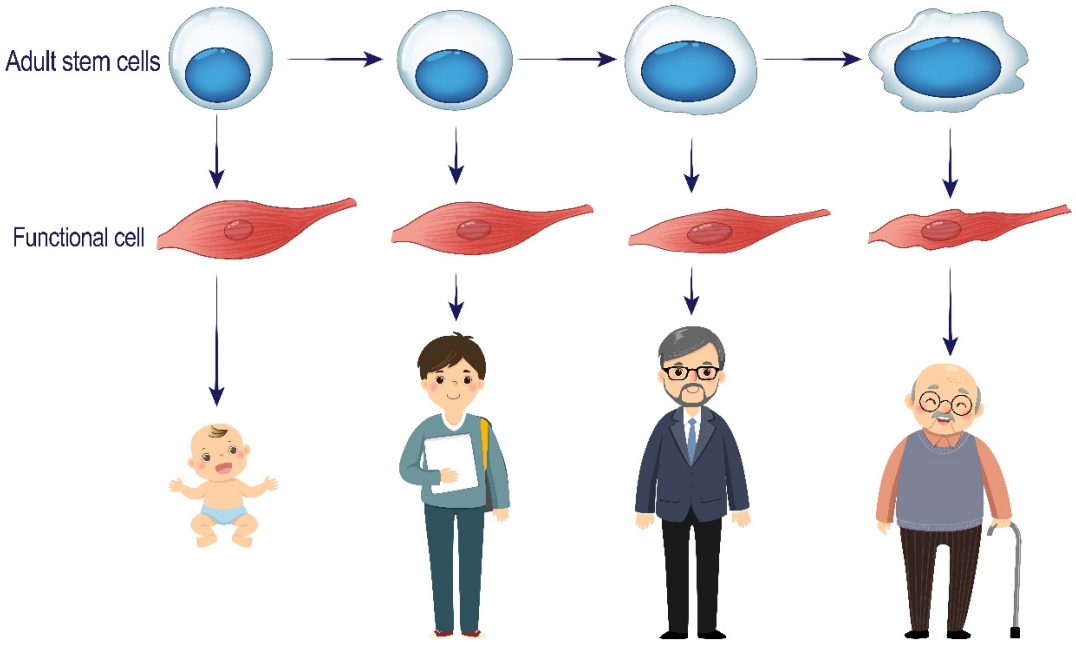

Figure 4. Each time adult stem cells divide, the daughter cells become more senescent than the previous generation. Functional cells differentiated from senescent adult stem cells are also senescent, leading to the progressive aging of tissues, organs, systems, and the organism. Adapted from a licensed iStock image.

8. Conclusions

Scientific theories must never allow ambiguity. Much like a coin placed on a table—it is either heads or tails—the same principle applies to theories of aging. In summary, the aging process is programmatically regulated, rather than resulting from the accumulation of random damage. To reverse individual aging, substantially extend lifespan, replace organ transplantation, and cure degenerative diseases, the most promising strategy at present is to lengthen the telomere and rDNA arrays of adult stem cells within tissues. This can drive rejuvenation at the tissue, organ, and whole-organism levels. Apart from this approach, all other anti-aging interventions can only achieve minor lifespan extension and are incapable of inducing true biological rejuvenation.

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Conflicts of Interest

Bilu Huang is the founder and chief scientific officer of Fuzhuang Therapeutics Co., Ltd., a biotech company working in this field. He also serves as an honorary unpaid scientific advisor to Fundación Canaria ALCASIV, a nonprofit foundation based in Spain.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the AI tool Doubao (Seed 2.1 Turbo) was used to assist with the translation of the original Chinese manuscript into English. After using this tool, the English translation was carefully reviewed and edited, and the author takes full responsibility for the content of the published article.

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