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Perspective

Feasibility Analysis of Mainstream Aging Theories and Intervention

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Abstract: Many aging theories are incorrect, which explains the lack of effective interventions and even the emergence of contradictory results. Here, we first briefly introduce the latest aging theory: the Telomere DNA and Ribosomal DNA Co-regulation Model for Cell Senescence (TRCS). We then conduct a critical analysis of several mainstream aging theories and their corresponding interventions. Our findings suggest that key aging theories—including the Epigenetic Theory, the Free Radical Theory, the Mitochondrial Theory, the Somatic Mutation Theory, the Autophagy Theory, and the Inflammation Theory of Aging—may be fundamentally flawed. This is because interventions derived from these theories—including the elimination of senescent cells and the infusion of young plasma—fail to significantly extend lifespan and, in some instances, have even been reported to accelerate aging.

Keywords: genetic program; cell senescence; rDNA; aging intervention; degenerative diseases

1. Introduction

We all grow old and eventually die. Moreover, many degenerative diseases are caused by aging. Therefore, instead of addressing different diseases separately, it is better to focus on solving the problem of aging. Although many theories of aging have been proposed, many of them are wrong, and thus there is a lack of effective interventions. To this end, this paper first briefly introduces the latest theory of aging—the Telomere DNA and Ribosomal DNA Co-regulation Model for Cell Senescence (TRCS), and then conducts a critical analysis of several mainstream aging theories and their corresponding interventions.

2. The Essence of Aging is a Program

Since each species of organisms has a relatively fixed timetable of growth, development, maturation, aging and death, the essence of aging is a genetic program, rather than random accumulation of damage. Because random accumulation of damage cannot explain why, when several killifish of the same genus with extremely similar body structures but different lifespans are placed in the same pond for artificial breeding, the difference in their lifespans still exists [1].

During the process of cellular aging, gene expression is also programmed. For example, in the aging process of hematopoietic stem cells, 1500 genes are upregulated and 1500 genes are downregulated [2]. According to this, the common anti-aging measures are to inhibit a certain upregulated gene or to activate or overexpress a certain downregulated gene. However, this kind of intervention at the metabolic level and signaling pathways can only slightly extend lifespan, and it has significant side effects. Moreover, it is fundamentally impossible to achieve rejuvenation.

Therefore, the fundamental cause of aging should not be sought in which genes are upregulated or downregulated, but in why these genes are upregulated or downregulated as age increases.

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3. Cellular Senescence is Co-Regulated by Telomere DNA and Ribosomal DNA through p53 Pathway

3.1. The Proposal of the Telomere DNA and Ribosomal DNA Co-Regulation Model for Cell Senescence (TRCS Model)

The primary manifestations of cellular senescence are as follows: with advancing age, the synthesis rates of total protein and ATP gradually decline, leading to functional degeneration. Moreover, in cells of the same differentiated type, the gene expression profile also changes progressively with age, resulting in altered cellular function. Accordingly, cellular senescence can be defined as the process by which cellular function gradually degenerates and changes over time. For example, the rate of total protein synthesis in mesenchymal stem cells (MSCs) decreases significantly with increasing passage number [3]. The rate of mitochondrial ATP production in human skeletal muscle declines with age [4]. Fetal hepatocytes express alpha-fetoprotein; after birth and into adulthood, they cease to express alpha-fetoprotein and instead express albumin. In old age, they gradually stop expressing albumin and switch to expressing another protein [5].

However, to enable the temporal programmed expression of a fixed set of genes on chromosomes, a timing substance (clock) is required to drive the genetic program. Telomeres, as multi-copy tandem repeat DNA sequences, are analogous to the sand in an hourglass and represent the best candidate for a timing substance.

Nevertheless, telomere shortening does not occur in many senescent cells; in some cases, telomeres even lengthen. In addition, chromosomes in terminally differentiated cells no longer replicate, so telomere shortening is negligible. Furthermore, cells eventually cease proliferation even when telomere length is stabilized by the introduction of telomerase mRNA [6]. Based on these observations, I hypothesize that, in addition to telomeres, another type of multi-copy tandem repeat DNA must act as a timing substance to drive the execution of the genetic program.

Accordingly, I proposed the Telomere DNA and ribosomal DNA co-regulation model for cell senescence (TRCS model) [7]. This theory holds that p53 binds to both telomeres and nucleoli [8,9], maintaining a balanced state between p53 synthesis and degradation. Therefore, as telomeres and/or rDNA arrays gradually shorten, this balance is disrupted, and p53 generates a concentration gradient along the time axis (Figure 1).

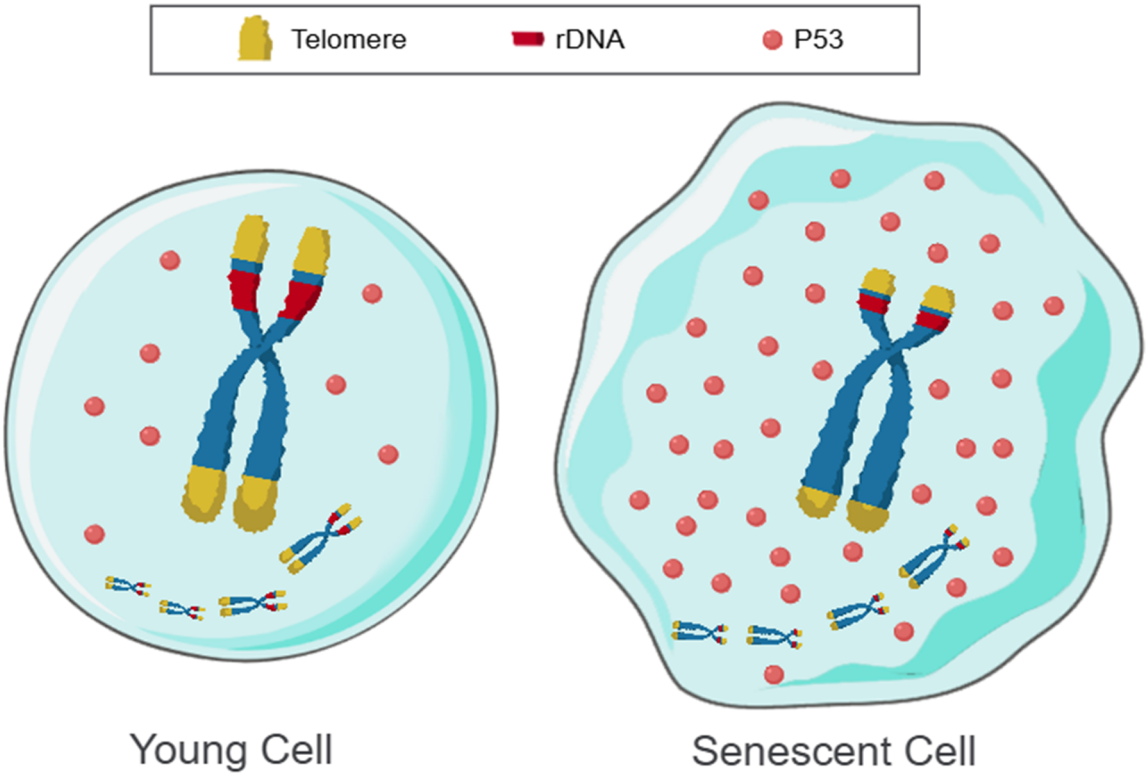

Figure 1. Telomere DNA and ribosomal DNA co-regulation model for cell senescence.

Left: Chromosomes with long arrays of telomeres and rDNA: P53 is rapidly degraded, P53 levels are low, and the cell is youthful. Right: Chromosomes with short arrays of telomeres and rDNA: P53 is slowly degraded, P53 levels are high, and the cell is aged. This figure is reproduced from Huang and Hu's Causality of Aging Hallmarks of Ref. [1] under the terms of the Creative Commons Attribution (CC BY) license.

Since p53 negatively regulates rDNA transcription and mitochondrial ATP production [10,11], and p53 also binds to the promoters and enhancers of various genes, the gradual formation of a p53 concentration gradient along the time axis leads to a progressive decline in the synthesis rates of total protein and ATP. Meanwhile, it upregulates the expression of some genes and downregulates others, thereby driving the temporally programmed expression of gene clusters on chromosomes and continuously altering the gene expression profile [1].

3.2. Relationship between Gene Expression Profiles and Age-Related Diseases

As the gene expression profile changes, the structure and function of cells and tissues are remodeled, thereby driving ontogeny, maturation, senescence, and age-related diseases. For example, in arteriosclerosis, phenotypic transformation of smooth muscle cells is accompanied by calcification, characterized by upregulation of the osteogenic transcription factor Cbfa1 (Runx2) and downregulation of smooth muscle lineage markers. This converts healthy, soft and elastic arteries into diseased arteriosclerotic vessels [12].

It has long been believed that low-density lipoprotein cholesterol (LDL-C), which contributes to atherosclerosis, can infiltrate the vascular wall only because the vascular wall is damaged, providing an opportunity for LDL-C entry. However, this is not the case. Studies have shown that SR-B1, a receptor that actively takes up LDL-C from the blood, is upregulated in senescent vascular endothelial cells, thereby increasing LDL-C uptake [13]. At the same time, senescent macrophages downregulate the expression of a transcription factor named TFEB, which in turn increases the level of p62—a protein that inhibits the lysosomal degradation of lipids in macrophages [14]. Thus, on the one hand, senescent vascular endothelial cells actively increase LDL-C uptake; on the other hand, senescent macrophages actively reduce lipid degradation. As a result, lipid uptake exceeds degradation, promoting plaque growth. Atherosclerosis and plaque formation are the major causes of hypertension and cardiovascular-cerebrovascular diseases.

In Alzheimer's disease (AD), the methylation level in the promoter region of the amyloid-β precursor protein (APP) decreases with advancing age [15], leading to upregulation of this gene. Meanwhile, the expression level of low-density lipoprotein receptor-related protein 1 (LRP1), which transports Aβ into the bloodstream across the blood-brain barrier, is downregulated with age [16]. Thus, Aβ production is increased on the one hand, and Aβ clearance is reduced on the other, gradually giving rise to the symptoms of AD.

Telomere length is negatively correlated with the expression of the DUX4 gene [17], and DUX4 is negatively correlated with the expression of the MHC-I gene. Therefore, with progressive telomere shortening, DUX4 expression is gradually upregulated while MHC-I expression is gradually downregulated, so that upregulation of DUX4 impairs antigen presentation by MHC [18], which compromises the clearance of mutated cells by the immune system. Accordingly, the shortening of telomeres and rDNA arrays is an important cause of increased accumulation of DNA mutations in cells and a higher incidence of tumors in individuals.

3.3. Validation of the TRCS Model

The TRCS model previously proposed [7] that shortening of telomeres and rDNA arrays leads to elevated p53 levels, and that the rejuvenation mechanism underlying pluripotent reprogramming is attributed to the substantial elongation of telomeres and rDNA arrays. Accordingly, knockdown of 45S rDNA copy number in primary mouse and human cells resulted in the expected significant upregulation of the senescence markers p53, p21, p16, and SA-β-GAL, as well as marked reductions in telomere length, cell viability, and cell passage number. In addition, examination of senescent mouse cells, hESCs, and hiPSCs revealed that senescent cells exhibited significantly decreased telomere length and 45S rDNA copy number, whereas hESCs and hiPSCs showed significant increases in both parameters. These data strongly demonstrate that the rejuvenation mechanism of hESCs and hiPSCs is not due to epigenetic reprogramming, but rather to the marked lengthening of both telomere DNA arrays and 45S rDNA arrays. Cellular senescence and the Hayflick limit are fundamentally co-regulated by telomeres and 45S rDNA, with rDNA contributing more heavily to senescence than telomeres (unpublished observations and future work is underway). From first principles, species lifespan is determined by the shortening rate of telomeres and/or rDNA arrays, which are influenced by both genetic and environmental factors.

The validity of a theory is determined by its self-consistency. Since the shortening of telomeres and rDNA arrays is the fundamental cause of cellular senescence and serves as the timing substance that drives the programmed expression of gene clusters, the telomeres and rDNA that are depleted in somatic cells must be replenished in germ cells or early embryonic cells; otherwise, life cannot be passed down through generations. Fortunately, evidence has shown that telomeres and rDNA depleted in somatic cells can be replenished in early embryonic cells or germ cells [19–21].

3.4. Mechanism Underlying the Anti-Aging Effect of Caloric Restriction (CR) Explained by the TRCS Model

It is generally believed that CR extends lifespan in animals by enhancing autophagy and reducing inflammation. However, these explanations may be incorrect, as many interventions that enhance autophagy and inhibit inflammation have failed to extend lifespan in mice.

Both telomeric DNA and nucleolar DNA are multi-copy tandem repeat arrays, which are inherently unstable. During transcription or replication, histones are removed to expose the DNA and unwind the double-stranded structure, making it susceptible to interference or damage from various factors, resulting in copy number loss. For example, metabolism promotes telomere transcription [22], and increased transcription of telomere DNA into RNA accelerates telomere shortening [23]. A nutrient-rich diet increases rDNA transcription by activating the mechanistic target of rapamycin (mTOR) [24], thereby accelerating rDNA array shortening in Drosophila [25]. Activation of mTORC1 leads to rDNA array shortening in mouse hematopoietic stem cells [26]. In other words, the transcription of telomeres and rDNA results in the shortening of telomere and rDNA arrays.

SIRT6 is a histone deacetylase localized to telomeres, nucleoli, and other regions [27]; it maintains hypoacetylation of histones associated with telomeres, rDNA, and other loci, and hypoacetylated histones bind tightly to DNA, thereby inhibiting the transcription of telomeres and rDNA. Therefore, SIRT6 knockout results in high-level transcription of rDNA in the nucleolus [28] and accelerated shortening of telomere and rDNA arrays. Accordingly, overexpression of SIRT6 slows the shortening rate of telomere and rDNA arrays, extending the median lifespan of male mice by 27% and female mice by 15% [29]. The anti-aging drug rapamycin can suppress rDNA transcription by inhibiting mTORC1, thus slowing the shortening of telomere and rDNA arrays. In the ovaries of rapamycin-treated rats, the protein expression of SIRT1 and SIRT6 is significantly increased, possibly by inhibiting the mTOR signaling pathway and activating the SIRT signaling pathway [30]. Caloric restriction (CR) also significantly elevates SIRT6 protein levels [31].

However, since overexpression of histone deacetylases such as SIRT6 inhibits rDNA transcription and protein synthesis, it suppresses cell proliferation and immune function, resulting in severe side effects. This makes them difficult to use as anti-aging drugs, and they are even less likely to reverse aging. For example, rapamycin inhibits immune function and suppresses cell renewal in the intestinal and oral mucosa, which are prone to wear and damage [32].

4. Feasibility Analysis of Mainstream Theories of Aging and Interventions

A correct theory does not allow for the existence of a loophole, and the more loopholes there are, the less reliable it is.

4.1. The Epigenetic Theory of Aging

With the increase of age, the level of DNA methylation in the whole genome will gradually decrease. Based on this, an epigenetic clock can be artificially assigned to measure physiological age [33]. In 2023, David A. Sinclair et al. [34] proposed the Information Theory of Aging (ITOA), which further described the types of epigenetic information loss during the aging process, including the reduction of DNA methylation, the dysregulation of transcription factors, non-coding RNA, chromatin structure changes, histone modifications and abundance. The ITOA holds that the loss of epigenetic information is an important cause of aging.

DNA demethylation and methylation, histone deacetylation and acetylation all occur simultaneously. Therefore, epigenetic modifications are dynamic and unstable, and do not possess the properties of a timing substance. Thus, the age-related changes in epigenetics cannot be the cause of aging, but are the result of the shortening of telomere DNA and rDNA arrays [35–37]. It is like wrinkles on the face are not the cause of skin aging, but the result of skin cell aging. Compared with senescent cells, young cells have longer telomeres, higher telomerase activity, and TERT has been proven to interact with chromatin remodeling factors and regulate DNA methylation [38]. Therefore, ITOA is a wrong theory and has been questioned by others [39,40].

The method of changing cellular epigenetics is called “epigenetic reprogramming”, which includes “pluripotent reprogramming”, “partial reprogramming”, and “direct reprogramming”. In pluripotent reprogramming, somatic cells lose their identity, and the epigenetic age (EpiAge) is reversed to 0 years. The “Telomere DNA and ribosomal DNA co-regulation model for cell senescence” speculates [7] that the fundamental reason why reprogramming rejuvenates cells is the significant elongation of telomeres and the rDNA array. Our experiment also found that, compared with senescent cells, the telomere length and 45S rDNA copy number of hESC and hiPSC were significantly increased. Therefore, the rejuvenation mechanism of hESC and hiPSC is not due to epigenetic reprogramming (unpublished observation).

Since the telomeres and rDNA array of iPSC and ESC do not shorten, these cells do not experience epigenetic aging [33]. When iPSC and ESC differentiate into somatic cells, telomeres begin to shorten rapidly [41]. As the epigenetic clock is regulated by telomeres and rDNA [35–37], the time when iPSC and ESC begin to differentiate is also the time when the epigenetic clock starts ticking quickly [42]. However, it has been found that the DNA of 72% of hiPSC is severely damaged, so the somatic cells differentiated from iPSC will be cleared by the immune system, which cannot be used to rejuvenate aging tissues or treat age-related degenerative diseases.

In partial reprogramming, cell identity remains unchanged, and telomeres are not elongated or slightly shortened. Once the expression of Yamanaka factors is halted, aging phenotypes rapidly reaccumulate. Specific data show that at 4 and 8 days after induction cessation, markers such as DNA damage, H3K9me3 levels, and nuclear envelope abnormalities gradually return to levels close to those of untreated cells [43].

Direct reprogramming, also known as transdifferentiation, directly converts aged fibroblasts into neural stem cells while preserving the aging phenotype, without reversing EpiAge [44], suggesting that direct reprogramming may not be a feasible approach for treating neurodegenerative diseases.

There is also ample evidence indicating that the epigenetic theory of aging is incorrect; for example, Altos Labs achieved only a 12% increase in the median lifespan of wild-type mice through partial reprogramming [45], which is inferior to small-molecule anti-aging drugs, and the reason for such a modest lifespan extension may be related to the promotion of cell regeneration by Yamanaka factors, such as the fact that promoting angiogenesis can significantly extend mouse lifespan [46], and partial reprogramming also increases cortical angiogenesis [47]. Doxycycline can promote cardiac regeneration after myocardial infarction in mice by activating the ATF4 signaling pathway [48], extend the lifespan of Caenorhabditis elegans by 72.8%, reduce lipofuscin (LF) content by approximately 50% [49], and extend the lifespan of progeroid mice [50]; the more senescent a cell is, the lower its DNA methylation level, yet the genome of primordial germ cells (PGCs) also contains very little methylated DNA [51], so does that mean PGCs are the most senescent cells? In fact, the opposite is true: PGCs, like iPS cells, have immortal potential. Aging in some animals is unrelated to methylation loss; for instance, DNA methylation is scarce or absent in Drosophila and other dipteran insects, and the widely studied aging model Caenorhabditis elegans also lacks DNA methylation. Steve Horvath, a professor of human genetics and biostatistics at the University of California, Los Angeles, stated that the National Institutes of Health has consistently supported him, but honestly, this is insufficient, because epigenetic clocks remain controversial—some researchers argue that if worms do not have an epigenetic clock, how can they age? This may complicate grant applications. Experiments have shown that the rejuvenation of cellular physiological status occurs prior to the rejuvenation of epigenetic signatures during reprogramming [52], suggesting that reprogramming-induced aging reversal is independent of epigenetic alterations; after partial reprogramming, telomeres are not elongated or are slightly shortened, senescent markers begin to accumulate again, and EpiAge reverts to the pre-reprogramming state [43]. Although continuous supplementation with alpha-ketoglutarate (AKG) for 7 months can set back EpiAge by 8 years [53], rigorous testing by the U.S. National Institute on Aging has not confirmed that AKG extends lifespan in male or female mice [54]. Growth hormone can reverse EpiAge [55], and trials in elderly individuals have shown that growth hormone supplementation increases muscle mass and thickens the skin in people aged 61–81 years, making them appear 10–20 years younger [56], yet long-term use of growth hormone actually accelerates aging [57–59]; a 60-year-old man who received growth hormone-releasing hormone (GHRH) gene therapy showed a 6-year reduction in EpiAge but a 7-month increase in telomere age compared with peers [60], indicating that some anti-aging drugs that reverse EpiAge, enhance mitochondrial function, and promote cell proliferation may actually deplete the limited number of cell divisions and lifespan, and EpiAge may only reflect metabolic rate.

Because telomere DNA and rDNA are fragile tandem repeat arrays, the transcription process can easily cause copy loss. Since the synthesis of proteins requires the prior synthesis of rRNA, which accounts for 82% of the total RNA, the paradox that growth hormone downregulates EpiAge while shortening lifespan is actually promoting protein and ATP synthesis. When tested, it shows a younger state, but in reality, it is overdrawing on the limited length of telomeres and the rDNA array. It is worth noting that many so-called anti-aging drugs that promote protein and ATP synthesis may also overdraw on lifespan. For example, the anti-aging drug NR, which increases NAD+, can enhance mitochondrial function. However, after the most rigorous test by the National Institute on Aging in the United States, it was found to shorten the lifespan of male mice by 3% [61]. In Caenorhabditis elegans, the addition of vitamin C increased mitochondrial ATP production by more than 2.5 times. On the eighth day after treatment, the content of lipofuscin (LF) increased by about 18%, and the lifespan was shortened [49].

Why does the level of DNA methylation in the whole genome gradually decrease with age?

DNA methyltransferase DNMT1 plays an important role in maintaining the state of DNA methylation. However, p53 can bind to the promoter of the DNMT1 gene [62]. Therefore, as the telomeres and rDNA arrays

gradually shorten, the level of p53 will gradually increase, which in turn leads to the gradual downregulation of DNMT1 gene expression and thus reduces the level of DNA methylation in the whole genome.

There is a chicken-and-egg question: does DNA methylation occur first and then lead to transcriptional silencing, or does transcriptional silencing occur first and then lead to DNA methylation?

Antisense lncRNA is usually transcribed from the antisense strand of a protein-coding gene and overlaps in sequence with the mRNA of that gene. About 70% of genes have antisense lncRNA, and the transcription of antisense lncRNA is often correlated with the transcription of the sense strand of its gene. When antisense lncRNA is transcribed, the DNA at that site is recognized by the active DNA demethylase TET3, which then removes the methylation modification at that site [63]. Therefore, it is the transcription factors that first promote DNA transcription, and during DNA transcription, the methylation is removed. In the absence of transcription factors, DNA is methylated again.

Although global genomic DNA methylation levels gradually decline with age, some genes such as IFNγ, F3, CRAT, and OGG become more highly methylated during aging, while GCR, iNOS, and TLR2 are more readily demethylated [64], and all these genes are associated with inflammation. In neurons of Alzheimer's disease patients, the methylation level of the promoter region of the amyloid precursor protein gene also decreases with age, leading to elevated expression of this gene and thus neurological dysfunction [15]. Notably, a recent study by Ziyu Lu, Wei Zhou, et al. investigated how cellular composition and gene regulation undergo systematic changes over time during mammalian aging, showing that aging is not random degeneration but a genetic program driven by specific molecular mechanisms [65]. The aging process of *Arabidopsis thaliana*, like that of mammals, follows a gradual decline in DNA methylation levels with advancing age. However, mutations in the *TCX5/6* genes maintain stable DNA methylation levels throughout the entire lifespan, yet the aging rate remains comparable to that of the wild type [66]. During aging, most somatic cells exhibit global DNA hypomethylation, whereas the aging of hematopoietic stem cells is characterized by global hypermethylation [67]. Nevertheless, deletion of the *GADD45B* gene also elevates DNA methylation levels in young hematopoietic stem cells, resulting in epigenetic profiles similar to those of aged hematopoietic stem cells. Notably, such methylation alterations do not lead to functional impairment of hematopoietic stem cells; their self-renewal and differentiation capacities remain intact [68].

These two lines of evidence clearly demonstrate that both the epigenetic theory of aging and the ITOA are incorrect. The loss of epigenetic information is more likely a consequence rather than a driving cause of aging. The programmed temporal expression of genes governing individual development, maturation, and aging is presumably driven by molecular clocks such as telomeres and/or rDNA, rather than by epigenetic regulation. Therefore, aging or neurodegenerative diseases are not a form of "random damage accumulation" or "random epigenetic information loss" [34], but a programmed genetic program.

In conclusion, the epigenetic theory of aging is wrong.

4.2. The Free Radical Theory of Aging

In 1956, Harman proposed the free radical theory of aging [69], a theory that is still being praised by some people to this day. However, to date, no free radical scavenger has been found to significantly extend the lifespan of mice.

Free radicals are mainly reactive oxygen species (ROS) produced in the mitochondria. ROS can attack various macromolecules, causing mutations in nuclear DNA and mtDNA, affecting the mobility of proteins within cells [70], and leading to telomere shortening [71]. For example, human fibroblasts cultured under an oxygen tension of 40% experience an increase in the rate of telomere shortening per cell division from the original 90 bp to 500 bp, and the number of passages decreases from 45 to just a few [72]. Neutrophils can induce telomere shortening in fibroblasts and hepatocytes in a ROS-dependent manner [73]. Therefore, in theory, ROS can promote individual aging. It is important to note that, in terms of causality, ROS is just one of many factors that affect the rate of aging, not the fundamental cause of aging.

However, the free radical theory of aging overlooks the fact that, during the course of hundreds of millions of years of evolution, individuals and cells have developed a complete and redundant defense system to overcome the various damages caused by ROS. First of all, in young tissues and cells, the components damaged by ROS can be quickly repaired or replaced, and thus do not pose a threat. In addition, individual aging is mainly caused by the replicative senescence of adult stem cells, which are mostly in a quiescent state and reside in hypoxic niches, and do not produce much ROS to begin with. For example, viable stem cells can be extracted from a corpse two weeks after death [74]. Moreover, a small amount of ROS plays an important physiological role in cells [75]. Therefore, over—scavenging ROS is actually harmful. For example, several common antioxidants seem to

increase mortality [76]. Besides, cells have a regulatory function to balance ROS. When ROS levels are artificially increased, the function of clearing ROS will be correspondingly enhanced.

- The following are several pieces of evidence that do not support the free radical theory of aging:Lipofuscin (LF) is hard-to-degrade waste produced by lysosomes, and ROS can promote the production of LF. In post—mitotic cells, the content of LF is higher than that in mitotic cells [77]. The skin of the elderly accumulates a large amount of LF, resulting in a visible aging appearance—age spots. In 1973, Tappel found that feeding adult mice with feed containing the antioxidant vitamin E for 1 year resulted in a definite reduction in neuronal LF, but there was no reduction in mortality [78]. Vitamin C is an effective antioxidant. Although vitamin C can extend the lifespan of progeroid mice, it has not been found to extend the lifespan of wild type mice [79]. In Caenorhabditis elegans treated with vitamin C, the content of LF increased by about 18%, and the lifespan was shortened [49]. This suggests that LF does not drive aging, and antioxidants do not extend lifespan.
- Methylene blue (MB) is a potent antioxidant that can penetrate organelles such as lysosomes and mitochondria, but it does not extend the average lifespan of mice [80]; α-lipoic acid is an antioxidant that effectively prevents lipid peroxidation to block the accumulation of its harmful byproducts, including toxic aldehydes such as acrolein. However, α-lipoic acid instead significantly shortens the median lifespan of mice [81]; overexpression of superoxide dismutase (SOD) also fails to extend mouse lifespan [82]; increasing reactive oxygen species (ROS) in lower organisms can instead extend both healthspan and maximum lifespan [83]; deletion of the mitochondrial superoxide dismutase gene sod-2 prolongs the lifespan of *Caenorhabditis elegans*, despite a significant increase in oxidatively damaged proteins [84].

There are many other pieces of evidence that do not support the free radical theory of aging, which are not listed one by one in this paper. In conclusion, the free radical theory of aging is wrong.

4.3. The Mitochondrial Theory of Aging

In 1980, Miquel et al. [85] proposed the mitochondrial theory of cellular aging, which posits that ROS generated by mitochondria can cause oxidative damage to mtDNA, lipids, and proteins within the cell. This damage leads to cellular, tissue, and organ dysfunction, ultimately accelerating the aging process.

However, proteins damaged by ROS can be degraded and renewed, and mutated mtDNA can also be selectively cleared [86]. On April 1, 2002, I published an article titled “Can We Live Forever?” in Science and Technology Daily, in which I wrote: “Abnormal or dysfunctional mitochondria will be recognized and engulfed by lysosomes” [87]. The selective engulfing of mutated mitochondria by lysosomes is called “mitophagy”, a term proposed by Lemasters in 2005 [88]. The reason why senescent cells accumulate mutated mtDNA is that during the aging process, the genetic program intentionally shuts down this solution.

In the leaf cells of *Elodea densa*, chloroplasts within nucleate protoplasts undergo a process of senescence and structural disintegration, whereas chloroplasts in anucleate protoplasts remain green and continue to accumulate starch [89]. In 1975, Wright and Hayflick transplanted young nuclei into enucleated aged cytoplasm, and the cells regained their youth and continued to divide according to the remaining number of divisions of the young nuclei. Conversely, when aged nuclei were transplanted into enucleated young cytoplasm, the cells exhibited an aging phenotype and the number of cell divisions was greatly reduced. These studies indicate that the site determining cellular aging is not the mitochondria, but the cell nucleus. In other words, the accumulation of mtDNA mutations cannot lead to cellular aging. Moreover, increasing telomere length can significantly elevate the number of cell divisions. When mice were treated with AAV expressing mouse TERT at the ages of 1 and 2 years old, their average lifespan was extended by 24% and 13%, respectively [90].

However, there is no evidence to suggest that promoting mitochondrial function can also increase the number of cell divisions and significantly extend the lifespan of mice.

Whether mtDNA mutations cause animal aging or are merely correlated with it is a matter of intense debate. The following are several pieces of evidence that do not support the mitochondrial theory of cellular aging:

- The mtDNA mutations in the oocytes of rhesus monkeys and humans do not accumulate with age [91]; Vermulst et al. [92] found that mice models with increased mtDNA mutations showed no signs of accelerated aging and did not have shortened lifespans; Heterozygous mutation of mouse mitochondrial superoxide dismutase (SOD2) led to increased oxidative damage and mtDNA mutations, but did not shorten the animals’ lifespans [93]; The main characteristic of mitochondrial dysfunction is a decrease in ATP production. However, when doxycycline was used to inhibit ATP production by the mitochondria in Caenorhabditis elegans, the lifespan of the treated group was extended by 72.8%. In contrast, treatment with vitamin C, which led to a 2.5—fold increase in ATP production, resulted in an approximately 18% increase in LF content within the worms’ bodies after 8 days of treatment, and accelerated aging [49].

- Cells and organisms have various solutions for clearing mutated mtDNA: During the reprogramming process, mtDNA mutations in heteroplasmic cells show a bimodal distribution, and after four divisions, they either quickly lose the mutations or acquire more. iPSCs with high—mutation heteroplasmy grow slowly, and their EpiAge increases. This suggests that in tissues, cells with high—mutation mtDNA cannot compete with healthy cells and will be eliminated [94]; Drosophila can selectively clear mitochondria containing mutated mtDNA in muscles through mitophagy [95]; Lysosomes can degrade damaged mitochondria, and when lysosome function is impaired or overwhelmed, fibroblasts and cardiomyocytes will excrete damaged mitochondria through exosomes [96]; Damaged mitochondria in neurons are selectively expelled outside the cell and then taken up and degraded by astrocytes [97]; During the differentiation process, stem cells allocate more defective mitochondria to the progenitor cells of daughter cells and more normal mitochondria to the stem cells of daughter cells [98].

There are many other pieces of evidence that do not support the mitochondrial theory of cellular aging, which are not listed one by one in this paper. In conclusion, the mitochondrial theory of aging is wrong.

4.4. The Somatic Mutation Theory of Aging

In 1959, Szilard proposed [99] that somatic cell DNA would continuously mutate and accumulate, which might lead to aging.

However, the theory overlooks the fact that, during the course of hundreds of millions of years of evolution, organisms have already found solutions to clear mutated somatic cells from individuals. First of all, an individual is composed of a large number of somatic cells, and not all of these cells will undergo mutation. For cells with DNA mutations: (1) repair; (2) if repair is not successful, initiate apoptosis; (3) if neither repair nor apoptosis occur, they will eventually be cleared by the immune system. Therefore, DNA mutations are not the cause of individual aging. The reason why mutated somatic cells accumulate in aging individuals is that, during the aging process, the genetic program intentionally shuts down the DNA repair mechanism and immune surveillance mechanism. Moreover, some plants can live for thousands of years, and many animals and plants that reproduce asexually have not become extinct despite their cells having undergone countless divisions due to DNA mutations and accumulation. The somatic mutation theory of aging also fails to explain why the short—lived Caenorhabditis elegans and the long—lived Greenland shark, which can live up to 400 years, have such a huge difference in lifespan.

The following are several pieces of evidence that do not support the theory of somatic mutation accumulation in individual aging:

- Senescent cells have only a small number of mutations in their nuclear DNA [100]; the accumulation of nuclear DNA mutations does not accelerate aging [101]; the nuclei of HeLa cells rapidly accumulate DNA damage [102]. However, the number of divisions of HeLa cells remains infinite.
- Ionizing radiation greatly increases the DNA mutation rate. However, low—dose ionizing radiation can actually extend the lifespan of fruit flies, house flies, rats and mice [103–106]; atomic bomb survivors live longer than average [107]. These studies all show that the theory of somatic mutation accumulation in individual aging is wrong.
- Ionizing radiation is associated with an aging phenotype but does not affect telomere length or EpiAge [42,106,108], indicating that the radiation-induced aging phenotype is not genuine aging but a cellular response to DNA damage; chronic, low-dose total-body irradiation in mice resulted in reduced myocyte number, decreased proliferative capacity, and an increased quiescent state with little effect on differentiation ability [109], suggesting that an increased cellular quiescent state can delay the time to reach the Hayflick limit and thereby extend lifespan in mice; radiation can trigger cardiac cells to revert to a healthier state [110]; the NASA Twins Study showed that while spaceflight led to telomere elongation in some peripheral blood cell populations, return to Earth caused rapid telomere shortening within 48 h and a return to near-baseline levels within several months [111]. Combined radiation exposure and muscle unloading also induced telomere elongation in mouse muscle stem cells (MuSCs) and myofiber nuclei, but telomere shortening was not observed after cessation of radiation; instead, the extended telomere length was retained and continued to increase [112]. These studies may explain why ionizing radiation can extend lifespan despite increasing the rate of DNA mutations.
- The DNA mutation rate is the same in non—dividing and frequently dividing cells [113]; although there is a large difference in lifespan and body size among different mammalian species, the somatic mutation burden at the end of life is only about 3 times different [114]; it is classically believed that the accumulation of DNA mutations to produce cancer is a slow process. However, killifish have a rapid reduction in thymus size, extensive accumulation of deleterious mutations and cancer production in a short period of time [115,116].

These studies show that the rate of DNA mutation accumulation is not related to the number of cell divisions and other factors, but may be related to immune system aging. This is because long—lived species can maintain the sensitivity of immune surveillance for a longer time, allowing mutant cells to be cleared in time.

- Recent studies have suggested that the accumulation of DNA damage may be the cause of increased EpiAge [117]. I think this is not correct, because HeLa cells can rapidly accumulate mutated DNA [102], but EpiAge does not increase; ionizing radiation also causes DNA damage, but EpiAge does not increase [42,108]; fruit trees use bud variation to breed new varieties by relying on gene mutations in the stem cells of plant meristematic tissues, but the EpiAge of stem cells in plant meristematic tissues does not increase [66]; more than 70% of detectable DNA damage in iPSC [118], but the EpiAge of iPSC is still zero years old [108].Is it true that the stronger the DNA repair capacity, the lower the DNA mutation rate, and the longer the lifespan? No, because cockroaches and tardigrades have super strong DNA repair capacity, but their lifespan is much shorter than that of humans. According to the TRCS model speculation [7], the lifespan of a species is determined by the shortening rate of telomeres and/or the rDNA array. For example, in fruit flies with a 40-day lifespan, the rDNA array is shortened by half [21].

There is a lot of evidence that does not support the theory of somatic mutation accumulation in individual aging, which is not listed one by one in this paper. In conclusion, the theory of somatic mutation accumulation in individual aging is wrong.

4.5. The Autophagy Theory of Aging

Autophagy refers to the process by which various dysfunctional organelles and waste materials in the cell are transported to lysosomes for degradation, thereby achieving recycling of waste. One theory of aging suggests that the accumulation of waste materials in cells may lead to aging and degenerative diseases, and that enhancing autophagy can intervene in aging and degenerative diseases.

Over the course of hundreds of millions of years of evolution, organisms have already found solutions to clear various waste materials and dysfunctional organelles from cells. The reason why senescent cells accumulate waste materials or dysfunctional organelles is that, during the aging process, the genetic program intentionally shuts down these solutions. In other words, it is aging that leads to the accumulation of waste materials, and it is aging that leads to degenerative diseases, not the accumulation of waste materials that causes aging or neurodegenerative diseases. For example, in the brains of Alzheimer's disease (AD) patients, there is a large accumulation of LF, misfolded β-amyloid (Aβ) and hyperphosphorylated tau protein. In 1973, Tappel found that feeding adult mice with feed containing vitamin E for 1 year resulted in a definite reduction in neuronal LF, but there was no reduction in mortality. Feeding for 9–15 weeks with feed containing 2% protein resulted in a large amount of LF formation in the nervous system, and then feeding with feed containing 25% protein reduced LF [119]. However, a high—protein diet accelerates aging.

Antibodies can effectively clear Aβ, but the improvement in AD symptoms is not significant [120–122], which indicates that the accumulation of waste materials such as Aβ is not the cause of AD. A 2018 analysis found that between 1998 and 2017, there were 146 unsuccessful medicines in clinical trials for Alzheimer's. In that same time frame, only 4 new medicines were approved to treat the symptoms of Alzheimer's disease. In other words, for every successful research project, about 37 failed to yield a new medicine—a 2.7 percent success rate [123]. If the direction is wrong, the effort is in vain.

New neurons come from the differentiation of neural stem cells. Aβ binds to albumin and is then transported to the liver for degradation [124]. Microglia can also clear a large amount of Aβ. Microglia come from the differentiation of bone marrow stem cells. Several types of cells that make up the blood—brain barrier also come from the differentiation of bone marrow stem cells. Therefore, the fundamental cause of AD is the aging of neural stem cells in the brain and the aging of liver stem cells and bone marrow stem cells away from the brain [125–127]. Therefore, AD is incurable, and drug development focusing on Aβ and Tau is doomed to be a waste of effort.

The following are several pieces of evidence that do not support the intervention of aging by enhancing autophagy:

- In some cases, enhancing autophagy is instead detrimental to health [128]; ovarian aging in mice is associated with increased autophagy in granulosa cells [129]. Chloroquine (CQ) is the only autophagy inhibitor approved by the U.S. Food and Drug Administration (FDA) [130], yet CQ has been shown to extend the maximum lifespan of rats by 13%, which is comparable to some of the best anti-aging drugs ever tested in mouse models [131]. Inhibiting autophagy in aged *Caenorhabditis elegans* extends lifespan by 50% [132], whereas increasing intestinal autophagy in *Caenorhabditis elegans* accelerates aging [133]. Resveratrol enhances neuronal autophagy [134] but instead promotes neuronal senescence and induces brain atrophy in lemurs [135,136].

There is a lot of evidence that does not support the intervention of aging by enhancing autophagy, which is not listed one by one in this paper. In conclusion, the measures to intervene in aging by enhancing autophagy are wrong.

4.6. The Inflammation Theory of Aging

The nuclei and mitochondria of senescent cells release dsRNA and cDNA into the cytoplasm. The cell, mistaking this for a viral infection, activates the innate immune response, producing a senescence—associated secretory phenotype (SASP) and sterile inflammation [137–140]. This is to summon immune cells to clear away the senescent cells. Therefore, in terms of causality, inflammation is just the result of cellular aging, not the cause of it. Inhibiting inflammation is not conducive to the immune system's clearance of senescent cells, nor does it extend the lifespan of an individual. In fact, it may even accelerate aging.

The following are several pieces of evidence that do not support the intervention of aging by inhibiting inflammation:

- Reverse transcriptase inhibitors (NRTIs) can inhibit the production of cDNA by the nucleus, but they have not extended the lifespan of wild—type mice [141]; the anti-aging drug NR, which can boost NAD+, can reduce the release of inflammatory factors by 52.6% [142], and the macrophage migration inhibitory factor antagonist (MIF098) can help macrophages move and reduce chronic inflammation in the body. However, after the most authoritative National Institute on Aging in the United States tested it, it was found that NR actually shortened the lifespan of male mice by 3%, and MIF098 could not extend the lifespan of mice [61]. A study of the Tsimane people in the Bolivian Amazon rainforest and the Orang Asli people in Malaysia found no significant association whatsoever between inflammatory aging scores and hypertension, diabetes, or even chronic kidney disease [143], potentially invalidating inflammation as one of the twelve hallmarks of aging [144].
- With increasing age, SASP becomes progressively elevated, whereas the rate of telomere shortening instead slows down [145]; senescent cells release SASP, and clearing senescent cells can reduce SASP, but senescent cell clearance has not been found to extend the lifespan of wild-type mice [146]; moreover, it has been reported that female mice in which senescent cells were cleared starting from young age exhibited accelerated aging [147]; increased EpiAge and telomere shortening have been observed after senescent cell clearance [148]; clearing senescent cells fails to reverse epigenetic age and even accelerates epigenetic aging, which challenges the assumption of using the epigenetic clock as an early indicator for the efficacy of anti-aging interventions and suggests that senescent cell clearance may in fact accelerate the aging process [149]; senescent cell clearance accelerates ovarian aging in aged female mice [150]. This is because the removal of senescent cells stimulates the replication and differentiation of surrounding young cells to fill the void left by the eliminated senescent cells, thereby accelerating the shortening of telomeres and rDNA arrays and inducing replicative senescence.
- The inflammatory environment produced by senescent cells can prevent stem cell proliferation. Daily treatment with the senescent cell clearance agents dasatinib and quercetin can reduce the number of SA-β-GAL + cells, reduce inflammation and accelerate stem cell proliferation [151]. Therefore, clearing senescent cells or reducing SASP through CD36 neutralization can accelerate the proliferation of stem cells, resulting in replicative senescence.
- Compared with short-lived shark species, the copy number of three gene families (TNF, TLR, LRRFIP) involved in activating the NF-kB signaling pathway is significantly increased in the extremely long-lived Greenland shark. The authors believe that the significant increase in inflammatory genes has led to an increase in immunity, which contributes to the extreme longevity of the Greenland shark [152].
- As an inflammatory factor, IL-11 can activate the ERK-AMPK-mTORC1 signaling pathway. Although inhibiting IL-11 with antibodies can significantly extend the lifespan of mice [153], this does not prove that inhibiting inflammation can extend lifespan. This is because inhibiting mTORC1 alone can significantly extend the lifespan of mice, which is equivalent to taking the mTORC1 inhibitor rapamycin.

In conclusion, the increase in senescent cells and SASP seems to put stem cells in a "quiescent state", thereby delaying the replicative senescence of stem cells. In contrast, clearing senescent cells and reducing SASP seems to activate stem cell proliferation and differentiation, promoting the replicative senescence of stem cells. Therefore, intervening in aging by inhibiting inflammation is wrong.

4.7. Anti-Aging by Injecting Young Blood

The idea of vampire therapy has existed since ancient times. Does young blood really have the effect of rejuvenation?

Obviously not. Cells cultured daily in laboratories using calf serum and fetal bovine serum still cannot escape the fate of senescence and death. In elderly mice given repeated injections of young plasma, with the control group receiving saline, the median lifespan was26.4 months in the plasma-treated group versus 27 months in the control group [154], showing a slight reduction in lifespan in the young plasma group. Mesenchymal stem cell lysates can inhibit inflammation. Rats were injected with young adipose-derived mesenchymal stem cell lysates for life starting at 12 months of age, with an average lifespan of 657 days compared with 715 days in the control group, resulting in a significant reduction in lifespan [155]. Infusions of blood or plasma also reduce NK cell activity, impair immune surveillance, and promote the proliferation and metastasis of tumor cells [156]. Allogeneic stem cell injection strongly suppresses the host immune system [157]. Therefore, attempting to extend lifespan using young blood, plasma, exosomes, and allogeneic stem cells will not promote health and longevity; instead, it will increase cancer risk and shorten lifespan.

The following are several pieces of evidence that do not support the anti-aging effects of young blood:

- When aging hematopoietic stem cells are transplanted into young bone marrow, although the entire transcriptome and gene expression status of the stem cells can be reversed to a young state, the DNA methylation pattern, regenerative capacity, and the ability to repair damage do not change due to the young microenvironment [158]. Young blood and a young microenvironment cannot improve the function of aged skeletal stem cells [159].
- Through surgery, the blood vessels of young and old mice can be connected together, a process called "heterochronic parabiosis". Compared to the 27% lifespan extension achieved by caloric restriction in mice [160], the 5% lifespan extension observed in old mice that are heterochronically parabiosed with young mice is not significant. The mechanism of this slight lifespan extension may not be related to the plasma of young mice but rather due to the fact that young mice provide old mice with young bone marrow stem cells, which is equivalent to a bone marrow transplant. It has been found that in the heterochronic parabiosis system, less than 5% of the hematopoietic stem cells in old mice come from young mice [161]. Since bone marrow stem cells can differentiate into various immune cells to replenish the immune system, smooth muscle cells and endothelial cells in blood vessels, endothelial cells and pericytes in the blood-brain barrier, microglia with scavenger functions in the brain, and endothelial cells of meningeal lymphatic vessels, transplanting young bone marrow can keep tissues such as the immune system, circulatory system, and nervous system in a youthful state [126]. For example, bone marrow transplantation can replace 90% of microglia in the brain and significantly improve AD symptoms [127]. It is worth noting that to avoid strong immune rejection, animals used in heterochronic parabiosis are inbred strains with very high genetic similarity, so it cannot be implemented in humans, because only identical twins have the same genes in humans.
- Although many studies have shown that the blood of young mice can restore the physiological age of old mice to a young state, give stem cells the ability to divide again, and promote the regeneration of muscle tissue and hepatocytes [162], why is it that old mice injected with young blood have a slightly shorter lifespan than the control group [154]? The answer is that the tissues of old mice emit substances such as SASP and Aβ that inhibit cell activity into the blood. These harmful substances temporarily inhibit the activity of young cells and increase physiological age. Therefore, after heterochronic parabiosis is stopped, physiological age will decrease again and return to the baseline level [163]. On the contrary, because young blood can stimulate cell activity, it temporarily gives aging cells a rejuvenated phenotype. In fact, this is overdrawing on the limited number of cell divisions and lifespan, which is why the lifespan of old mice injected with young plasma is slightly shorter than that of the control group. Therefore, the way to extend lifespan is to keep adult stem cells in tissues in a "quiescent" state, rather than an active "proliferative" state.
- Recently, Pavel Borsky et al. [164] found that although plasma exchange therapy reduced levels of total cholesterol, non-HDL cholesterol, and triglycerides, levels of proteins such as albumin also decreased significantly. Measurements based on epigenetic clocks revealed no significant anti-aging effects; instead, an increase in certain aging biomarkers was observed. The results indicate that plasma exchange did not demonstrate anti-aging effects and may even accelerate epigenetic aging.

In conclusion, it is not feasible to intervene in aging by injecting young blood and heterologous stem cells. In summary, the mainstream theories of aging and their intervention effects are shown in Table 1.

Table 1. Mainstream theories of aging and intervention effects.

No.	Aging Theory	Interventions and Experimental Results
1	Epigenetics	Partial reprogramming only extends the median lifespan of mice by 12% [46], which is less effective than small-molecule anti-aging drugs. Once partial reprogramming is discontinued, aging phenotypes rapidly accumulate back to their original state [44].

Table 1. *Cont.*

No.	Aging Theory	Interventions and Experimental Results
2	Free radicals	The antioxidant methylene blue failed to extend the average lifespan of mice [80], whereas α-lipoic acid significantly shortened their median lifespan [81].
3	Mitochondria	Increasing mtDNA mutations does not shorten lifespan [92]; although antioxidants can reduce mtDNA mutations, they still fail to extend the lifespan of mice [78].
4	Somatic mutations	Increasing nuclear DNA mutations does not accelerate human aging [101]; ionizing radiation increases DNA mutations but does not elevate EpiAge [108]. Although antioxidants can reduce DNA mutations, they still fail to extend lifespan [78].
5	Autophagy	Resveratrol, which enhances autophagy, paradoxically promotes neuronal senescence and induces brain atrophy in lemurs [135,136]; chloroquine, which inhibits autophagy, significantly extends the maximum lifespan of rats [131].
6	Chronic inflammation	NR reduced the release of inflammatory factors by 52.6% [142], and MIF098 alleviated chronic inflammation in vivo. However, NR conversely shortened the lifespan of male mice by 3%, and MIF098 also failed to extend mice lifespan [61].
7	Accumulation of senescent cells	Clearing senescent cells failed to extend the lifespan of wild-type mice [146], and even accelerated telomere shortening and epigenetic aging [148].
8	Body fluid (blood)	Mice receiving multiple injections of young plasma showed a slightly shorter lifespan compared with the control group [154]; lifelong injection of lysate from young adipose-derived mesenchymal stem cells in rats resulted in a significantly shortened lifespan [155].

5. Conclusions

In summary, the current mainstream theories of aging are full of loopholes, and thus there are no effective measures to intervene in aging. From the perspective of the theory of aging as a program and the first principles, the lifespan of a species is determined by the rate of shortening of telomeres and/or the rDNA array. Interventions that "reconstruct the telomere/rDNA array" can achieve cellular rejuvenation and point the way for the development of reverse-aging drugs.

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Conflicts of Interest

The author declares no conflict of interest. Bilu Huang is the founder and chief scientific officer of Fuzhuang Therapeutics Co., Ltd., a biotech company working in this area.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the author used Doubao to assist in the translation of the manuscript from Chinese to English. After using this tool, the content was reviewed and verified for accuracy, and the author takes full responsibility for the content of the published article.

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