Biomedicine Advances

Biomedicine Advances. 2025;2(4):173-182
doi: 10.34172/bma.38
https://biomedad.ae

Review Article

A shift in architecture of aging: Cellular pathways and molecular networks

Nesa Kozali[1#], **AmirHossein FassihRamandi**[1#], **Sara Pahlavan**[2*]

[1]Faculty of Sciences and Advanced Technologies in Biology, University of Science and Culture, Tehran, Iran
[2]Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran

*__Corresponding Author:__ Sara Pahlavan, Email: sarapahlavan@Royaninstitute.org

[#]These authors contributed equally.

Summary

Aging is a multifactorial process driven by interconnected hallmarks that progressively compromise cellular and tissue function. Among the most recognized contributors are genomic instability, telomere attrition, epigenetic alterations, chromatin remodeling defects, loss of proteostasis, and impaired autophagy. Additional hallmarks include mitochondrial dysfunction, stem cell exhaustion, cellular senescence, deregulated nutrient-sensing, altered intercellular communication, chronic inflammation, and dysbiosis. Each hallmark not only manifests with age but also accelerates aging when exacerbated, while targeted interventions can slow or even reverse their effects. Collectively, these mechanisms establish a unifying framework to explain organismal aging, its links to age-related diseases, and the therapeutic prospects of approaches which are designed to enhance longevity and health-span. This review discusses the findings on the key cellular and molecular hallmarks of senescence with a focus on telomere attrition, epigenetic alterations, mitochondrial dysfunction and stem cell exhaustion.

Keywords: Senescence, Longevity, Stem cell exhaustion, Telomere attrition, Mitochondrial dysfunction

Received: August 9, 2025, **Revised:** September 14, 2025, **Accepted:** September 28, 2025, **ePublished:** October 20, 2025

Introduction

Aging research focuses on the progressive loss of function in organisms during adulthood. Since the original 2013 hallmarks of aging publication, nearly 300,000 studies have been added, which signals a need to update this framework with new perspectives.

While hallmarks of aging are interrelated, they must satisfy three key criteria: they develop over time, they can be enhanced experimentally to accelerate aging, and they can be targeted therapeutically which slows or reverses aging. This review focuses on the molecular, cellular, and systemic processes underlying these changes. Biological aging is assessed using physiological tests, functional evaluations, and advanced "omics" techniques, allowing a close look on the decline of health and treatment effects. The nine hallmarks initially proposed—such as genomic instability, telomere attrition, and cellular senescence—remain relevant but require revision based on recent mammalian studies (Figure 1).

Genomic Instability

The stability and integrity of the genome are constantly challenged by both external and internal factors. Externally, the genome is exposed to chemical agents, physical radiation, and biological damage. Internally, it faces threats such as replication errors, improper chromosome segregation, oxidative damage, and spontaneous hydrolytic events. These diverse sources of genomic stress can lead to a wide variety of genetic alterations, including: point mutations, gene deletions, chromosomal translocations, telomere attrition, single- and double-stranded DNA breaks, chromosomal rearrangements, nuclear structural defects, and gene disruptions due to viral or transposon insertions. Such molecular damage and the resulting genomic mosaicism are thought to contribute to both physiological aging and age-related diseases. To cope with these challenges, organisms have evolved sophisticated DNA repair and maintenance systems that safeguard the integrity of both nuclear and mitochondrial DNA. These systems also help maintain proper chromosomal structure and genomic stability. However, with growing age, the efficiency of these DNA repair mechanisms declines. This leads to the progressive accumulation of genetic damage and the abnormal accumulation of DNA in the cytoplasm, further driving cellular dysfunction and the aging process.[1]

Telomere Attrition

Damage at chromosome ends, known as telomere shortening, plays a key role in aging and related diseases. Because DNA polymerases are unable to replicate telomeres entirely, these sequences become progressively shorter with each cell division, eventually leading to genomic instability, senescence, or apoptosis. Telomerase, a ribonucleoprotein enzyme with reverse-transcriptase

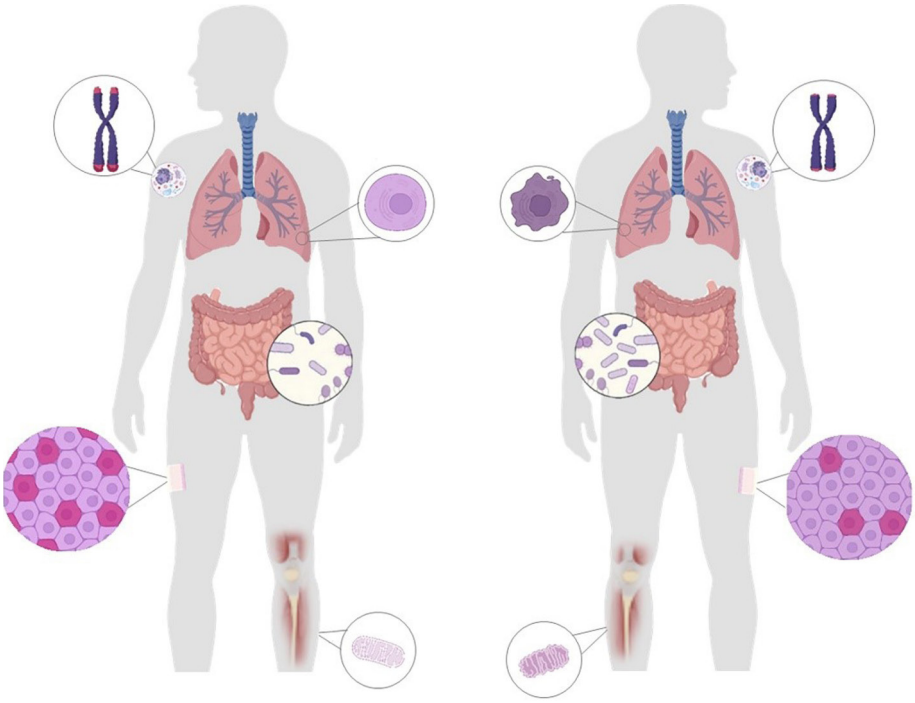

Figure 1. Key cellular and molecular hallmarks of aging. Telomere attrition, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, dysbiosis. The left scheme shows an individual with no senescence hallmarks individual and the right scheme displays an individual altered by aging-related mechanisms.

activity, reverses this process by extending telomeres. However, most adult somatic cells lack active telomerase, leading to continuous telomere erosion over time.

Interestingly, while genomic instability promotes cancer, telomere shortening can suppress tumor growth by limiting cell proliferation, making it a distinct hallmark of aging. Telomerase deficiency in humans is linked to premature disorders like pulmonary fibrosis and aplastic anemia, which disrupt tissue regeneration. Telomere length is affected by age, genetics, lifestyle, and cell division rates, and has been shown to predict lifespan across species. In addition to shortening, dysfunction of the shelterin proteins, which protect telomeres, can also trigger aging symptoms even when telomere length appears normal. Mouse models confirm that shorter telomeres decrease lifespan and accelerate aging, while lengthened telomeres enhance health and longevity. Notably, reactivating telomerase in telomerase-deficient mice reverses signs of premature aging. Similarly, telomerase activation, pharmacologically or via gene therapy, has shown benefits in extending lifespan and improving cognitive function in models of Alzheimer's disease.[1,2]

Telomerase and telomere-binding proteins: their roles within telomeres and beyond

Telomeres of mammalian cells consist of tandem repeats of the TTAGGG sequence that shorten progressively with each cell division. A certain minimum number of these repeats are crucial for shelterin proteins to bind and prevent activation of the DNA damage response (DDR) on chromosome ends. Telomerase, an enzyme that can extend telomeres, is mostly inactive in somatic cells but active in stem cells and cancer cells. While its reactivation may delay aging-related tissue degeneration, it can also promote uncontrolled cell proliferation in tumors, depending on how well the DDR pathway is maintained.

In addition, telomerase also plays roles beyond this, such as modulating the Wnt–β-catenin signaling pathway and acting as an RNA-dependent RNA polymerase.[3]

Telomerase Activation to Decelerate Aging and Treat Telomere Diseases

Short telomeres are a hallmark of aging and are linked, directly to the onset of age-related diseases. Mutations in telomerase or telomere-binding proteins lead to telomere dysfunction, which contributes to telomere syndromes, disorders marked by impaired tissue regeneration and fibrotic diseases.[4] Experimental models have shown that either telomerase deficiency or deletion of telomere-protective proteins like TRF1 in mouse kidney exacerbates fibrosis by triggering epithelial-to-mesenchymal transition (EMT), suggesting a direct role of telomere shortening in promoting age-related tissue damage.[4] More broadly, telomere dysfunction promotes senescence of cells, which accumulates with age and contributes to systemic decline and the development of multiple chronic diseases.[5] In the context of pulmonary fibrosis, a fatal lung disease associated with short telomeres, therapeutic delivery of telomerase via AAV9 vectors specifically targeting alveolar type II cells, has been shown to improve lung function, reduce inflammation, and reverse fibrosis

in mice. This treatment not only extends telomere length but also reduces DNA damage, apoptosis, and senescence in affected cells [6]. These findings collectively support the potential of telomerase activation as a method of reversing aging and treating telomere-mediated disease.

Epigenetic Alterations

Epigenetic alterations play a significant role in the aging process, including diverse mechanisms such as disrupted DNA methylation patterns, abnormal post-translational histone modifications, impaired chromatin remodeling, and deregulation of non-coding RNAs (ncRNAs). These changes, that are often reversible, act as key regulators of gene expression and other cellular functions and therefore contribute to the initiation and progression of multiple age-related diseases, including cancer, neurodegenerative disorders, metabolic syndrome, and skeletal pathologies. The establishment and maintenance of epigenetic marks rely on a complex network of enzymes, including DNA methyltransferases; histone acetyltransferases and deacetylases; histone methyltransferases and demethylases; and particular protein complexes addressing chromatin remodeling, along with the ncRNA synthesis and maturation.[1]

Non-Coding RNAs

Non-coding RNAs (ncRNAs) regulate critical processes of aging, like oxidative stress, mitochondrial injury, and inflammation. They also advance diseases such as cardiac diseases including arrhythmias, hypertrophy, fibrosis, and heart failure.[7]

Cellular senescence and organismal aging involve extensive molecular and morphological changes, and long noncoding RNAs (lncRNAs) are progressively recognized to act as nuclear structure modifiers. Certain lncRNAs are involved in the formation and maintenance of nuclear structure, and their expression gets modulated with age. RNA–DNA triplex formation enables lncRNAs to interact with specific genomic loci, linking DNA and proteins to alter nuclear organization. These mechanisms play a crucial role, however often under-recognized in nuclear morphology changes associated with aging. Advances in artificial intelligence and genetic perturbation technology offer highly promising tools to uncover direct cause-and-effect relationships.[8]

Circular RNAs (circRNAs) are stable, closed-loop RNAs with diverse functions including protein interaction, miRNA sponging, protein coding, and gene regulation. Their stability and detectability render them potential biomarkers for aging and age-related diseases. CircRNA abundance increases with age across species and may have implications in aging and cellular senescence. In particular, ciRS-7/circCDR1as is implicated in Alzheimer's disease, and circSfl in long lifespan in fruit flies. It is important to find functional circRNAs to reveal their functions in aging and age-related diseases.[9] Type H bone vessels, which are essential for angiogenesis-osteogenesis coupling, are decreased with age. This is caused by elevated microRNA-188-3p, which suppresses vessel formation by decreasing integrin β3 in endothelial cells. Knockdown of miR-188-3p in mice blocks age-related vessel loss, but overexpression causes bone aging by decreasing vessel density, bone mass, and the ability to repair them.[10]

Chromatin Remodeling

ATP-dependent chromatin remodelers control vital functions like transcription, replication, and DNA repair. According to the loss of heterochromatin model, regions created early in development deteriorate more and more with age, leading to abnormal transcription, gene de-repression, and genomic instability. Heterochromatin protein 1α (HP1α) and Polycomb group proteins are examples of molecular participants that maintain chromatin structure and DNA repair; as they age, they lose their ability to do so, which results in heterochromatin loss and uncontrolled gene expression.

Invertebrates with HP1α overexpression have longer lifespans than those with loss. In mammals, disorders such as PIN1 deficiency are associated with reduced heterochromatin integrity, which is linked to neurodegenerative disease and early aging. In human studies, disturbed SWI/SNF and Polycomb are also associated with cancer risk, neurodegenerative disease, and defective stem cell function. Therefore, preserving heterochromatin structure is a preferred strategy for genome preservation.[11]

Derepression of Retrotransposons

Genomes of nearly all organisms contain repetitive sequences produced by transposable elements (transposons), mobile genetic elements capable of moving within the genome and often amplifying to high copy numbers. While much of our knowledge of these elements comes from their germline activity seen in genome sequences, recent research shows that they are also active in somatic tissues throughout life. One of these elements, retrotransposons, has coevolved with host genomes since the earliest stages of life, usually in a competitive relationship that earned them names like "junk DNA" and "molecular parasites". There are significant connections between human physiology, health, and illness and retrotransposons activity and the molecular mechanisms that underlie it.[12] Although its effects are unknown, aging-induced loss of heterochromatin derepresses LINE-1 retrotransposons. Heterochromatin loss and senescence are caused by early LINE-1 RNA expression suppressing SUV39H1 activity in progeroid syndromes. In a mouse model of progeria, LINE-1 RNA silencing with antisense oligonucleotides decreased senescence gene expression, restored heterochromatin marks, and increased lifespan. These findings point to LINE-1 RNA as a possible target

for treatment in cases of premature aging.[13]

Loss of Proteostasis

Aging is a major risk factor for many illnesses, especially neurodegenerative conditions like Parkinson's and Alzheimer's disease. The loss of protein homeostasis, or proteostasis, which results in the buildup of protein aggregates, is a common characteristic of these disorders. By regulating synthesis, folding, structural stability, and degradation, a complex proteostasis network made up of molecular chaperones, proteolytic systems, and their regulators, healthy cell preserves protein balance. As we age, accumulated internal and external stressors put this system under strain, reducing its capacity and endangering the proteome's integrity. This deterioration contributes to the development of disease and is particularly harmful to post-mitotic cells, such as neurons. Proteome-wide analyses in aging have guided strategies to improve proteostasis, and pharmacological treatments aimed at fortifying this network have the potential to delay age-related proteome deterioration and extend health span.[14]

Disabled Macroautophagy

The cellular process known as macroautophagy, or simply "autophagy", encloses parts of the cytoplasm in double-membrane structures called autophagosomes. Later, these vesicles combine with lysosomes to decompose and recycle their contents. Although autophagy is essential for maintaining proteostasis, it also breaks down whole organelles as well as non-protein macromolecules like lipid droplets, glycogen, and cytosolic DNA. Particular types include reticulophagy for the endoplasmic reticulum, pexophagy for peroxisomes, lysophagy for lysosomes, and mitophagy for damaged mitochondria. Furthermore, autophagy aids in cell defense by eliminating invasive pathogens via xenophagy.[15]

One of the key mechanisms behind aging is the age-related decline in autophagy, which reduces the turnover of cellular organelles and it is one of the main mechanisms behind aging. It's crucial to remember that the genes and proteins involved in autophagy also take part in other degradation processes, such as the phagocytosis of extracellular materials by LC3 and the exosphere-mediated removal of intracellular waste, like malfunctioning mitochondria, which is subsequently eliminated by macrophages. Despite this overlap, there is compelling evidence that aging is directly related to the basic autophagy process.[1,16]

Deregulated Nutrient Sensing

The nutrient-sensing network, conserved through evolution, includes hormones like insulin, signaling pathways (PI3K-AKT, Ras-MEK-ERK), and transcription factors such as FOXOs. In order to control important cellular functions like autophagy, protein synthesis, metabolism, and mitochondrial function, the mTORC1 complex senses nutrients and stress. Depending on stress and nutrient availability, this network strikes a balance between cell defense and growth. In a variety of animal models, it has been demonstrated that reducing its activity genetically prolongs lifespan and health.[17,18]

Genetic studies in humans have linked the FOXO3 transcription factor and variants of genes in the nutrient-sensing network to increased human longevity. Furthermore, nutrient-sensing pathways are linked to epigenetic age in human cells.[17,19,20] This signaling network promotes healthy anabolic (growth) processes in youth, but it can also lead to aging as an adult. The pituitary gland's production of growth hormone (GH) is at the heart of the somatotrophic axis, a crucial pathway in the regulation of aging. Through GH receptors, GH causes liver cells to release IGFs, particularly IGF1. By activating its receptor (IGF1R), which sets off trophic signals via the PI3K-AKT and mTORC1 pathways, IGF1 subsequently stimulates growth and development.[21] Reducing somatotrophic pathway activity, either naturally or through engineered mutations, scientists prolonged life and slow the decline associated with aging in a number of animal models. Inhibiting this pathway from early adulthood improves general health even though defects in it cause dwarfism.

The ALK receptor tyrosine kinase is involved in another nutrient-sensing pathway. It is triggered by feeding in mice and reacts to the ligands Aug-a and Aug-b. Fruit flies' lifespan is prolonged, primarily in females, by inhibiting ALK, which also lowers fat and insulin-like peptides. Loss-of-function ALK mutations are associated with leanness in humans, and deleting ALK in mice increases resistance to diet-induced obesity. ALK is therefore a viable target for treatments related to metabolic aging.

Drugs like rapamycin that block mTORC1, extend lifespan even when started late in life and are being investigated as anti-aging treatments.[22] In mice, rapamycin improves various aspects of health, but it can worsen some age-related conditions like cataracts. It also provides protection in models of neurodegenerative and other age-related diseases. Elderly humans are more vulnerable to viral respiratory infections. However, pre-treatment with mTORC1 inhibitors has been shown to boost immune responses to flu vaccines in older adults and reduce respiratory infections during the following winter, indicating a viable strategy to halt age-related immune decline.[23]

Mitochondrial Dysfunction

Organismal aging involves a gradual decline in cellular performance and the deterioration of multiple tissues, reducing function and increasing mortality risk. Mitochondria, beyond their function as energy producers, is now recognized as key players in aging-related diseases such as neurodegeneration and cardiovascular disorders. There is evidence that aging is caused by an imbalance between the supply and demand of energy, which may be corrected by interventions such as calorie restriction,

exercise, and natural substances that act on pathways linked to conserved longevity.[21] In addition to being the main source of energy for the cell, mitochondria may also be the first to cause inflammation and cell death. While the release of caspase activators, nucleases, or other destructive enzymes from the intermembrane space can start pathways leading to programmed cell death, the release of mitochondrial DNA or reactive oxygen species (ROS) can activate inflammasomes or cytosolic DNA sensors.[24]

Mitochondrial Function and Longevity

Aging is marked by a slow deterioration of the body's homeostatic balance, leading to an increased susceptibility to a wide range of disorders. Aging is frequently associated with mitochondrial dysfunction. In a Drosophila model of muscle mitochondrial injury, researchers discovered that mild mitochondrial stress in muscle can preserve mitochondrial function, slow age-related decline in muscle performance and structure, and extend lifespan. Two important compensatory signaling pathways are responsible for this longevity benefit: a systemic pathway involving the Drosophila equivalent of insulin-like growth factor-binding protein 7, which suppresses insulin signaling and promotes mitophagy, and a muscle-specific, redox-dependent activation of genes governing the mitochondrial unfolded protein response (UPRmt).[25]

Age-related diseases, such as cardiac dysfunction, are becoming increasingly prevalent. Proton leakage in the heart mitochondria directly increases in naturally aged mice and rats, and ANT1 is the main mediator of this increased permeability, according to studies. Tetra-peptide SS-31 treatment prevents excessive proton entry, decreases permeability transition pore opening and mitochondrial flash activity, restores mitochondrial function by directly interacting with ANT1 and the ATP synthasome, and dramatically reverses diastolic dysfunction.[26]

In order to decouple nutrient oxidation from ATP synthesis and release the proton gradient as heat, lipophilic weak acids known as mitochondrial uncouplers move protons across the inner mitochondrial membrane without the assistance of ATP synthase.[27] This increases proton influx into the matrix, lowers mitochondrial membrane potential, and reduces oxygen radical formation. According to the "uncoupling to survive" hypothesis, such mild uncoupling can promote longevity by lowering oxidative stress and enhancing mitochondrial function.[28]

Moderate mitochondrial uncoupling reduces ROS production, delays age-related conditions like hepatic steatosis and diabetes, and prolongs lifespan, according to experimental evidence from yeast, worms, flies, rodents, and dogs. For instance, mice given a low dose of 2,4-dinitrophenol (DNP) have better tissue respiration, lower fasting glucose, insulin, and lipid levels, less oxidative stress, and longer lifespans.[29]

Despite its anti-aging potential, DNP's limited therapeutic range restricts its clinical applicability.[19] Reduction in mitochondrial content through suppression of the mitochondrial protein import system, known as MitoMISS, promotes a unique longevity mechanism. This process activates the mitochondrial unfolded protein response, driving an adaptive metabolic reprogramming. Enhanced glycolysis and de novo serine biosynthesis are directly linked to lifespan extension, whereas the induction of mitochondrial chaperones is not required for this longevity effect.[30]

Mitochondrial Microproteins and Aging

Humanin is a peptide derived from the mitochondria, with strong neuroprotective and cytoprotective effects, conserved across species. Its overexpression in *C. elegans*, through the daf-16/Foxo pathway, prolongs lifespan while in transgenic and humanin analogue HNG-treated mice, it enhances metabolic health, lowers inflammation, and guards against toxic damage. Although humanin levels typically decrease with age in most species, they remain constant in the long-lived naked mole-rat and are higher in children of centenarians. Humanin is linked to a longer lifespan and greater resistance to aging-related decline, as lower levels are linked to age-related illnesses like Alzheimer's and MELAS.[31]

Studies reveal that the growth hormone/insulin-like growth factor-1 (GH/IGF) axis, which has an inverse relationship with circulating humanin levels, is one of the endocrine pathways that regulate aging. Humanin levels are lower in short-lived GH-transgenic mice and higher in long-lived, GH-deficient Ames mice. Humanin levels are decreased in both mice and humans when GH or IGF-I is administered. These results suggest that humanin integrates mitochondrial function into the endocrine regulation of longevity by acting as a circulating signal derived from the mitochondria that influences the aging process.[32]

Mitochondrial-encoded MOTS-c, a peptide produced which is generated from the independent mitochondrial genome, has been shown to enhance physical performance in young, middle-aged, and old mice. It regulates nuclear genes related to metabolism and proteostasis, modulates skeletal muscle metabolism, and supports myoblast adaptation to metabolic stress. Intermittent MOTS-c treatment (three times per week) increases physical capacity and health-span in mice. In humans, exercise naturally stimulates MOTS-c expression in skeletal muscle and circulating blood.[33]

Cellular Senescence

Cellular senescence which is triggered by acute or chronic damage, increases significantly by getting older, affecting various cell types, especially fibroblasts, endothelial cells, and immune cells. Telomere shortening is one of the factors contributing to this process. Even non-dividing tissues

such as the heart and brain can accumulate senescent cells, and they also concentrate in particular areas when a disease is present.[34] Researches on mice has demonstrated that pharmacological or genetic removal of these cells can extend lifespan and health span.[35] Such clearance also leads to better results in multiple disease models. Several clinical trials are now exploring senescence-targeting treatments for human health conditions.[36] Primary senescence can be triggered by various factors such as oncogenic signaling, DNA damage, infections, mitochondrial dysfunction, oxidative stress, nutrient imbalance, mechanical stress, and critically short telomeres. Inflammatory and fibrotic signals such as TGF-β, IL-1β, IL-6, IL-8, and CCL2 cause secondary (paracrine) senescence.[37] Although these two forms have some characteristics in common, it is unclear how they differ molecularly. Senescence is marked by stable proliferative arrest, mainly through TP53 and CDKN2A/p16 pathways, which inhibit CDKs and E2F transcription factors.[38] This arrest is strengthened by the loss of lamin B1 and the reorganization of heterochromatin into SAHFs.[39] Depending on molecular context, cancer cells may undergo stable, reversible, or bypassed senescence after genotoxic stress. Senescence also plays a role in embryonic development by selectively eliminating specific cells.

Stem Cell Exhaustion

Stem cell exhaustion is a fundamental factor in aging, which results from the progressive decline in both the quantity and quality of adult stem cells. Stem cells are extremely sensitive and many circumstances can disrupt their homeostasis, resulting in decreased proliferation, a crucial indicator of stem cell aging.[40] Regeneration and tissue homeostasis depend on these cells and because of that, their decline over time severely limits the body's ability to repair damage, ultimately contributing to functional deterioration and age-related diseases.[1,41]

Adult stem cells have key role in tissue maintenance, repair, and regeneration throughout life [42]. In almost every tissue, stem cell exhaustion, characterized by decreased quantity and function, occurs with aging, and each has a unique renewal strategy.[43] In hematopoietic stem cells (HSCs), age-related shifts in differentiation reduce adaptive immune cell production, increasing risks of anemia and myeloid malignancies.[44] A number of age-related illnesses and uncommon genetic conditions are also associated with this kind of exhaustion. These include deregulated HSC function in FA, impaired neuronal differentiation and DNA repair in neural stem cells in Parkinson's disease and xeroderma pigmentosum, and premature mesenchymal stem cell loss in Hutchinson-Gilford progeria syndrome, Werner syndrome, and Fanconi anemia.[45]

Rejuvenation of Tissue Repair by Reprogramming

Cellular reprogramming toward pluripotency includes converting adult somatic cells into induced pluripotent stem cells (iPSCs) by the coordinated action of four transcription factors, OCT4, SOX2, KLF4, and MYC (OSKM).[46] This process begins with the suppression of cell identity genes and activation of pluripotency genes, often spanning several weeks.[47] In addition to altering cell identity, complete reprogramming causes cellular rejuvenation, which is indicated by decreased p16,[48] telomere extension,[49] and DNA methylation clock reset.[50] Partial, transient, or intermediate reprogramming[51-54] can repair DNA damage, reset DNA methylation, and restore youthful epigenetic and transcriptomic patterns *in vitro* and *in vivo*. Even if reprogramming is stopped early, rejuvenation occurs gradually. In mice, transient reprogramming enhances tissue repair capacity enabling aged tissues to recover from damage as efficiently as young tissues, demonstrated in the pancreas,[52] skeletal muscle,[52] nerve fibers, eye,[53] skin,[51] heart,[55] and liver.[56] It is possible to partially reverse age-related dysfunctions like memory deterioration, loss of hippocampus neurogenesis,[57] and diminished vision.[53] Applications during repair, such as in traumatic brain injury[58] and skin wound healing,[59] have also shown benefits. Lifespan extension has been achieved in progeroid mice,[52] though not yet in wild-type mice.

Partial reprogramming mirrors natural tissue repair, where cells transiently de-differentiate, acquire progenitor-like traits, and then re-differentiate.[60] Natural repair processes may also involve rejuvenation, supported by evidence that the epigenetic clock accelerates after injury and partially reverses during repair.[61] Tissue injury may create a microenvironment favorable to IL-6-driven reprogramming.[62] Additionally, cyclic FOXM1 expression extends lifespan in both progeroid and wild-type mice,[63] likely by promoting de-differentiation and proliferation of kidney epithelial cells during repair process.[64] These collaborations between artificial reprogramming and natural repair indicates potential strategies to restore regenerative capacity in aging tissues.

Stems Cells and the Pathway to Aging and Cancer

The ability of tissues to maintain homeostasis and regenerate declines with aging, positioning stem cell deterioration as a key contributor to the aging process. The extent to which this decline drives aging, as opposed to broader systemic tissue and organ degeneration, likely varies among different tissues and their resident stem cells. However, there is substantial evidence linking stem cell dysfunction to several age-related pathologies. Aging is also associated with a higher incidence of cancer, which usually requires the accumulation of multiple mutations over time. Stem cells, due to their capacity for self-renewal and differentiation, are prime spots for precancerous mutations, and can pass them to both self-renewing progeny and differentiated cells throughout life. Tumor suppressor proteins act as safeguards by inducing

apoptosis or permanent growth arrest in potentially malignant clones, but the ongoing demands of tissue maintenance can cause these pathways to inadvertently deplete stem cells, thereby contributing to aging.[65]

As aging progresses, certain stem cell clones can gain a competitive advantage over others while still remaining under the regulatory influence of systemic factors and the local stem cell niche. Many molecular changes linked to stem cell aging also occur in tumors of older individuals. Studying these alterations in stem and progenitor cells may provide significant understanding into cancer development and help identify new therapeutic options. Various cancers including those of the colon, breast, brain, head and neck, pancreas, and blood, harbor small populations of tumor-initiating cells, known as cancer stem cells (CSCs). These CSCs share key characteristics with normal stem cells, such as unlimited self-renewal capacity, and can generate most or all cell types within a tumor. By sustaining tumor growth and maintenance, CSCs play a central role in cancer persistence.[65]

The overlap in molecular pathways governing normal stem cell maintenance and oncogenesis highlight the dual challenge of preserving stem cell function while preventing malignant progression. Future therapeutic strategies will need to precisely target the mechanisms of stem cell aging, both to restore tissue homeostasis and to reduce cancer risk, without compromising the essential self-renewal capacity required for lifelong regeneration.

Metabolism and Epigenetic

Recent studies underscore metabolism as a major factor in stem cell aging, with growing evidence that metabolic signaling pathways are closely linked to the aging process. Moreover, cellular metabolic activity can influence epigenetic states, which in turn affect the overall organismal aging and longevity.[41,66] Metabolic and epigenetic regulation are closely connected, especially in stem cells. However, their combined role in maintaining cell function and balance is not yet fully understood. Many cofactors for epigenetic enzymes that drive DNA and histone modifications are metabolites derived from cellular metabolism, meaning metabolic changes triggered by environmental cues can directly influence the stem cell epigenome, function, and senescence. Pathways such as sirtuins, mTOR, and insulin–FOXO link metabolism to chromatin regulation. SIRT1, for instance, senses NAD^+ levels to control stem cell fate, while SIRT6 and SIRT7 maintain redox balance and mitochondrial stress responses; their decline with age impairs stem cell homeostasis. NRF2, a key regulator of antioxidants, is also disrupted during aging. when restored, it has shown to rescue premature stem cell attrition in progeroid models. FOXO3 maintains stem cell quiescence and supports autophagy, whereas mTOR promotes activation in nutrient-rich states but can accelerate senescence if autophagy is dysregulated. Metabolites themselves act as epigenetic regulators: NAD^+ depletion with age increases histone acetylation and shifts muscle stem cells from fatty acid oxidation to glycolysis. α-Ketoglutarate supports DNA/histone demethylation, influencing stem cell differentiation.

SAM levels, linked to one-carbon metabolism, adjust histone methylation and change with age. These pathways illustrate that metabolic state not only fuels stem cells but also reshapes their epigenetic landscape. This influences aging, the risk of diseases, and potential to regenerate. Understanding this interaction could help develop therapies to preserve stem cell function and extend health-span.[41,67]

Altered Intercellular Communication

Aging is accompanied by progressive changes in intercellular communication, disrupting homeostatic and adaptive regulation. These include impairments in neural, neuroendocrine, and hormonal signaling systems such as adrenergic, dopaminergic, insulin/IGF-1, renin-angiotensin, and sex hormones, often linked to reproductive decline.[21,68] While many of these changes originate from intrinsic cellular processes, including those driven by the senescence-associated secretory phenotype (SASP), they form a distinct hallmark of aging together. This hallmark connects cell-intrinsic changes to meta-cellular effects like chronic inflammation, reduced immune surveillance, and altered genome–microbiome communication leading to dysbiosis. Research in this field explores pro-aging and pro-longevity blood-borne factors, intercellular signaling pathways, and the impact of extracellular matrix (ECM) degradation on aging.[1]

Chronic Inflammation

Inflammation increases gradually during aging and the process is known as "inflammaging" which manifests both systemically and locally, contributing to conditions such as arteriosclerosis, neuroinflammation, osteoarthritis, and intervertebral disc degeneration. Circulating inflammatory cytokines and biomarkers, including CRP, increase with age and all-cause mortality in older populations is strongly predicted by elevated plasma IL-6.[69] As inflammation increases, immune function declines, which can be seen in altered myeloid and lymphoid cell profiles.[70] A distinct group of age-associated T cells (Taa) consisting of exhausted memory cells, arise and stimulates inflammation through the release of granzyme K. Age-related changes in T cell subsets also lead to hyperactive pro-inflammatory TH1 and TH17 cells. These changes impair the immunosurveillance against infected, malignant, or senescent cells. They also reduce self-tolerance, raising the risk of autoimmune diseases, and weaken the maintenance of biological barriers.[71] Collectively, these changes fuel chronic and systemic inflammation, increasing vulnerability to disease in aging individuals.[1]

Dysbiosis

In recent years, researchers have identified the gut microbiome as a crucial regulator of diverse physiological functions, including nutrient digestion and absorption, pathogen defense, and the production of vital metabolites such as vitamins, amino acid derivatives, secondary bile acids, and short-chain fatty acids (SCFAs). The gut microbiome also interacts with the peripheral and central nervous systems and other organs, playing a vital role in overall health. Disruption of this bidirectional host–microbe interaction leads to dysbiosis, contributing to conditions like obesity, type 2 diabetes, ulcerative colitis, neurological disorders, cardiovascular diseases, and cancer. Growing evidence has sparked intense interest in understanding how the gut microbiota alters as we age.[24,72]

Conclusion

Aging is considered a physiological phenomenon, but some aging-related diseases can accelerate senescence and result in premature death. Therefore, understanding the cellular and molecular mechanisms of aging empower the health system in controlling or preventing early onset age-related diseases. From this prospective, it is crucial to deepen our knowledge of aging mechanisms and how to reverse it for therapeutic purposes. Advancements in genomics, transcriptomic. proteomics and metabolomics will revolutionize our understanding of mechanistic aspects of aging and the therapeutic targets. It is anticipated that this century will be a turning point for many age-related diseases such as neurodegenerative disorders and cardiovascular diseases. Therefore, it is crucial to enhance our efforts toward unfolding cellular and molecular mechanisms of aging.

Acknowledgements

The authors would like to thank Science and Culture University for their support.

Authors' Contribution

Conceptualization: Sara Pahlavan.
Supervision: Sara Pahlavan.
Writing–original draft: Nesa Kozali, AmirHossein FassihRamandi.
Writing–review & editing: Sara Pahlavan.

Competing Interests

The authors declare no conflict of interest.

Ethical Approval

Not Applicable.

Funding

None.

Intelligence Use Disclosure

This article has not utilized artificial intelligence (AI) tools for research and manuscript development, as per the GAMER reporting guideline.

References

1. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. Cell. 2023;186(2):243-78. doi: 10.1016/j.cell.2022.11.001.
2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6):1194-217. doi: 10.1016/j.cell.2013.05.039.
3. Martínez P, Blasco MA. Telomeric and extra-telomeric roles for telomerase and the telomere-binding proteins. Nat Rev Cancer. 2011;11(3):161-76. doi: 10.1038/nrc3025.
4. Saraswati S, Martínez P, Graña-Castro O, Blasco MA. Short and dysfunctional telomeres sensitize the kidneys to develop fibrosis. Nat Aging. 2021;1(3):269-83. doi: 10.1038/s43587-021-00040-8.
5. Rossiello F, Jurk D, Passos JF, d'Adda di Fagagna F. Telomere dysfunction in ageing and age-related diseases. Nat Cell Biol. 2022;24(2):135-47. doi: 10.1038/s41556-022-00842-x.
6. Povedano JM, Martinez P, Serrano R, Tejera Á, Gómez-López G, Bobadilla M, et al. Therapeutic effects of telomerase in mice with pulmonary fibrosis induced by damage to the lungs and short telomeres. Elife. 2018;7:e31299. doi: 10.7554/eLife.31299.
7. Jusic A, Thomas PB, Wettinger SB, Dogan S, Farrugia R, Gaetano C, et al. Noncoding RNAs in age-related cardiovascular diseases. Ageing Res Rev. 2022;77:101610. doi: 10.1016/j.arr.2022.101610.
8. Han JJ. LncRNAs: the missing link to senescence nuclear architecture. Trends Biochem Sci. 2023;48(7):618-28. doi: 10.1016/j.tibs.2023.03.007.
9. Kim E, Kim YK, Lee SV. Emerging functions of circular RNA in aging. Trends Genet. 2021;37(9):819-29. doi: 10.1016/j.tig.2021.04.014.
10. He WZ, Yang M, Jiang Y, He C, Sun YC, Liu L, et al. miR-188-3p targets skeletal endothelium coupling of angiogenesis and osteogenesis during ageing. Cell Death Dis. 2022;13(5):494. doi: 10.1038/s41419-022-04902-w.
11. Swer PB, Sharma R. ATP-dependent chromatin remodelers in ageing and age-related disorders. Biogerontology. 2021;22(1):1-17. doi: 10.1007/s10522-020-09899-3.
12. Gorbunova V, Seluanov A, Mita P, McKerrow W, Fenyö D, Boeke JD, et al. The role of retrotransposable elements in ageing and age-associated diseases. Nature. 2021;596(7870):43-53. doi: 10.1038/s41586-021-03542-y.
13. Della Valle F, Reddy P, Yamamoto M, Liu P, Saera-Vila A, Bensaddek D, et al. LINE-1 RNA causes heterochromatin erosion and is a target for amelioration of senescent phenotypes in progeroid syndromes. Sci Transl Med. 2022;14(657):eabl6057. doi: 10.1126/scitranslmed.abl6057.
14. Hipp MS, Kasturi P, Hartl FU. The proteostasis network and its decline in ageing. Nat Rev Mol Cell Biol. 2019;20(7):421-35. doi: 10.1038/s41580-019-0101-y.
15. Levine B, Kroemer G. Biological functions of autophagy genes: a disease perspective. Cell. 2019;176(1-2):11-42. doi: 10.1016/j.cell.2018.09.048.
16. Nicolás-Ávila JA, Lechuga-Vieco AV, Esteban-Martínez L, Sánchez-Díaz M, Díaz-García E, Santiago DJ, et al. A network of macrophages supports mitochondrial homeostasis in the heart. Cell. 2020;183(1):94-109.e23. doi: 10.1016/j.cell.2020.08.031.
17. Slack C, Alic N, Foley A, Cabecinha M, Hoddinott MP, Partridge L. The Ras-Erk-ETS-signaling pathway is a drug target for longevity. Cell. 2015;162(1):72-83. doi: 10.1016/j.cell.2015.06.023.
18. Singh PP, Demmitt BA, Nath RD, Brunet A. The genetics of aging: a vertebrate perspective. Cell. 2019;177(1):200-20. doi: 10.1016/j.cell.2019.02.038.
19. Ji JS, Liu L, Shu C, Yan LL, Zeng Y. Sex difference and interaction of SIRT1 and FOXO3 candidate longevity genes

on life expectancy: a 10-year prospective longitudinal cohort study. J Gerontol A Biol Sci Med Sci. 2022;77(8):1557-63. doi: 10.1093/gerona/glab378.
20. Kabacik S, Lowe D, Fransen L, Leonard M, Ang SL, Whiteman C, et al. The relationship between epigenetic age and the hallmarks of aging in human cells. Nat Aging. 2022;2(6):484-93. doi: 10.1038/s43587-022-00220-0.
21. Amorim JA, Coppotelli G, Rolo AP, Palmeira CM, Ross JM, Sinclair DA. Mitochondrial and metabolic dysfunction in ageing and age-related diseases. Nat Rev Endocrinol. 2022;18(4):243-58. doi: 10.1038/s41574-021-00626-7.
22. Orthofer M, Valsesia A, Mägi R, Wang QP, Kaczanowska J, Kozieradzki I, et al. Identification of ALK in thinness. Cell. 2020;181(6):1246-62.e22. doi: 10.1016/j.cell.2020.04.034.
23. Mannick JB, Teo G, Bernardo P, Quinn D, Russell K, Klickstein L, et al. Targeting the biology of ageing with mTOR inhibitors to improve immune function in older adults: phase 2b and phase 3 randomised trials. Lancet Healthy Longev. 2021;2(5):e250-62. doi: 10.1016/s2666-7568(21)00062-3.
24. López-Otín C, Kroemer G. Hallmarks of health. Cell. 2021;184(1):33-63. doi: 10.1016/j.cell.2020.11.034.
25. Owusu-Ansah E, Song W, Perrimon N. Muscle mitohormesis promotes longevity via systemic repression of insulin signaling. Cell. 2013;155(3):699-712. doi: 10.1016/j.cell.2013.09.021.
26. Zhang H, Alder NN, Wang W, Szeto H, Marcinek DJ, Rabinovitch PS. Reduction of elevated proton leak rejuvenates mitochondria in the aged cardiomyocyte. Elife. 2020;9:e60827. doi: 10.7554/eLife.60827.
27. Childress ES, Alexopoulos SJ, Hoehn KL, Santos WL. Small molecule mitochondrial uncouplers and their therapeutic potential. J Med Chem. 2018;61(11):4641-55. doi: 10.1021/acs.jmedchem.7b01182.
28. Brand MD. Uncoupling to survive? The role of mitochondrial inefficiency in ageing. Exp Gerontol. 2000;35(6-7):811-20. doi: 10.1016/s0531-5565(00)00135-2.
29. Barros MH, Bandy B, Tahara EB, Kowaltowski AJ. Higher respiratory activity decreases mitochondrial reactive oxygen release and increases life span in *Saccharomyces cerevisiae*. J Biol Chem. 2004;279(48):49883-8. doi: 10.1074/jbc.M408918200.
30. Lionaki E, Gkikas I, Daskalaki I, Ioannidi MK, Klapa MI, Tavernarakis N. Mitochondrial protein import determines lifespan through metabolic reprogramming and de novo serine biosynthesis. Nat Commun. 2022;13(1):651. doi: 10.1038/s41467-022-28272-1.
31. Yen K, Mehta HH, Kim SJ, Lue Y, Hoang J, Guerrero N, et al. The mitochondrial derived peptide humanin is a regulator of lifespan and healthspan. Aging (Albany NY). 2020;12(12):11185-99. doi: 10.18632/aging.103534.
32. Lee C, Wan J, Miyazaki B, Fang Y, Guevara-Aguirre J, Yen K, et al. IGF-I regulates the age-dependent signaling peptide humanin. Aging Cell. 2014;13(5):958-61. doi: 10.1111/acel.12243.
33. Reynolds JC, Lai RW, Woodhead JS, Joly JH, Mitchell CJ, Cameron-Smith D, et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. Nat Commun. 2021;12(1):470. doi: 10.1038/s41467-020-20790-0.
34. Mehdizadeh M, Aguilar M, Thorin E, Ferbeyre G, Nattel S. The role of cellular senescence in cardiac disease: basic biology and clinical relevance. Nat Rev Cardiol. 2022;19(4):250-64. doi: 10.1038/s41569-021-00624-2.
35. Robbins PD, Jurk D, Khosla S, Kirkland JL, LeBrasseur NK, Miller JD, et al. Senolytic drugs: reducing senescent cell viability to extend health span. Annu Rev Pharmacol Toxicol. 2021;61:779-803. doi: 10.1146/annurev-pharmtox-050120-105018.
36. Wissler Gerdes EO, Misra A, Netto JM, Tchkonia T, Kirkland JL. Strategies for late phase preclinical and early clinical trials of senolytics. Mech Ageing Dev. 2021;200:111591. doi: 10.1016/j.mad.2021.111591.
37. Birch J, Gil J. Senescence and the SASP: many therapeutic avenues. Genes Dev. 2020;34(23-24):1565-76. doi: 10.1101/gad.343129.120.
38. Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. Cellular senescence: defining a path forward. Cell. 2019;179(4):813-27. doi: 10.1016/j.cell.2019.10.005.
39. Sati S, Bonev B, Szabo Q, Jost D, Bensadoun P, Serra F, et al. 4D genome rewiring during oncogene-induced and replicative senescence. Mol Cell. 2020;78(3):522-38.e9. doi: 10.1016/j.molcel.2020.03.007.
40. Rossi DJ, Bryder D, Seita J, Nussenzweig A, Hoeijmakers J, Weissman IL. Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature. 2007;447(7145):725-9. doi: 10.1038/nature05862.
41. Ren R, Ocampo A, Liu GH, Izpisua Belmonte JC. Regulation of stem cell aging by metabolism and epigenetics. Cell Metab. 2017;26(3):460-74. doi: 10.1016/j.cmet.2017.07.019.
42. Goodell MA, Rando TA. Stem cells and healthy aging. Science. 2015;350(6265):1199-204. doi: 10.1126/science.aab3388.
43. Molofsky AV, Slutsky SG, Joseph NM, He S, Pardal R, Krishnamurthy J, et al. Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. Nature. 2006;443(7110):448-52. doi: 10.1038/nature05091.
44. Conboy IM, Rando TA. Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches. Cell Cycle. 2012;11(12):2260-7. doi: 10.4161/cc.20437.
45. Shaw AC, Joshi S, Greenwood H, Panda A, Lord JM. Aging of the innate immune system. Curr Opin Immunol. 2010;22(4):507-13. doi: 10.1016/j.coi.2010.05.003. Liu GH, Barkho BZ, Ruiz S, Diep D, Qu J, Yang SL, et al. Recapitulation of premature ageing with iPSCs from Hutchinson-Gilford progeria syndrome. Nature. 2011;472(7342):221-5. doi: 10.1038/nature09879.
46. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663-76. doi: 10.1016/j.cell.2006.07.024.
47. Deng W, Jacobson EC, Collier AJ, Plath K. The transcription factor code in iPSC reprogramming. Curr Opin Genet Dev. 2021;70:89-96. doi: 10.1016/j.gde.2021.06.003.
48. Li H, Collado M, Villasante A, Strati K, Ortega S, Cañamero M, et al. The Ink4/Arf locus is a barrier for iPS cell reprogramming. Nature. 2009;460(7259):1136-9. doi: 10.1038/nature08290.
49. Marion RM, Strati K, Li H, Tejera A, Schoeftner S, Ortega S, et al. Telomeres acquire embryonic stem cell characteristics in induced pluripotent stem cells. Cell Stem Cell. 2009;4(2):141-54. doi: 10.1016/j.stem.2008.12.010.
50. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14(10):R115. doi: 10.1186/gb-2013-14-10-r115.
51. Browder KC, Reddy P, Yamamoto M, Haghani A, Guillen IG, Sahu S, et al. In vivo partial reprogramming alters age-associated molecular changes during physiological aging in mice. Nat Aging. 2022;2(3):243-53. doi: 10.1038/s43587-022-00183-2.
52. Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, et al. In vivo amelioration of age-associated hallmarks by partial reprogramming. Cell. 2016;167(7):1719-33.e12. doi: 10.1016/j.cell.2016.11.052.
53. Lu Y, Brommer B, Tian X, Krishnan A, Meer M, Wang C, et al. Reprogramming to recover youthful epigenetic information

and restore vision. Nature. 2020;588(7836):124-9. doi: 10.1038/s41586-020-2975-4.
54. Gill D, Parry A, Santos F, Okkenhaug H, Todd CD, Hernando-Herraez I, et al. Multi-omic rejuvenation of human cells by maturation phase transient reprogramming. Elife. 2022;11:e71624. doi: 10.7554/eLife.71624.
55. Chen Y, Lüttmann FF, Schoger E, Schöler HR, Zelarayán LC, Kim KP, et al. Reversible reprogramming of cardiomyocytes to a fetal state drives heart regeneration in mice. Science. 2021;373(6562):1537-40. doi: 10.1126/science.abg5159.
56. Hishida T, Yamamoto M, Hishida-Nozaki Y, Shao C, Huang L, Wang C, et al. In vivo partial cellular reprogramming enhances liver plasticity and regeneration. Cell Rep. 2022;39(4):110730. doi: 10.1016/j.celrep.2022.110730.
57. Rodríguez-Matellán A, Alcazar N, Hernández F, Serrano M, Ávila J. In vivo reprogramming ameliorates aging features in dentate gyrus cells and improves memory in mice. Stem Cell Reports. 2020;15(5):1056-66. doi: 10.1016/j.stemcr.2020.09.010.
58. Gao X, Wang X, Xiong W, Chen J. In vivo reprogramming reactive glia into iPSCs to produce new neurons in the cortex following traumatic brain injury. Sci Rep. 2016;6:22490. doi: 10.1038/srep22490.
59. Doeser MC, Schöler HR, Wu G. Reduction of fibrosis and scar formation by partial reprogramming in vivo. Stem Cells. 2018;36(8):1216-25. doi: 10.1002/stem.2842.
60. Roux AE, Zhang C, Paw J, Zavala-Solorio J, Malahias E, Vijay T, et al. Diverse partial reprogramming strategies restore youthful gene expression and transiently suppress cell identity. Cell Syst. 2022;13(7):574-87.e11. doi: 10.1016/j.cels.2022.05.002.
61. Poganik JR, Zhang B, Baht GS, Tyshkovskiy A, Deik A, Kerepesi C, et al. Biological age is increased by stress and restored upon recovery. Cell Metab. 2023;35(5):807-20.e5. doi: 10.1016/j.cmet.2023.03.015.
62. Mosteiro L, Pantoja C, Alcazar N, Marión RM, Chondronasiou D, Rovira M, et al. Tissue damage and senescence provide critical signals for cellular reprogramming in vivo. Science. 2016;354(6315):aaf4445. doi: 10.1126/science.aaf4445.
63. Ribeiro R, Macedo JC, Costa M, Ustiyan V, Shindyapina AV, Tyshkovskiy A, et al. In vivo cyclic induction of the FOXM1 transcription factor delays natural and progeroid aging phenotypes and extends healthspan. Nat Aging. 2022;2(5):397-411. doi: 10.1038/s43587-022-00209-9.
64. Chang-Panesso M, Kadyrov FF, Lalli M, Wu H, Ikeda S, Kefaloyianni E, et al. FOXM1 drives proximal tubule proliferation during repair from acute ischemic kidney injury. J Clin Invest. 2019;129(12):5501-17. doi: 10.1172/jci125519.
65. Rossi DJ, Jamieson CH, Weissman IL. Stems cells and the pathways to aging and cancer. Cell. 2008;132(4):681-96. doi: 10.1016/j.cell.2008.01.036.
66. Yang J, Li J, Suzuki K, Liu X, Wu J, Zhang W, et al. Genetic enhancement in cultured human adult stem cells conferred by a single nucleotide recoding. Cell Res. 2017;27(9):1178-81. doi: 10.1038/cr.2017.86.
67. Berger SL, Sassone-Corsi P. Metabolic signaling to chromatin. Cold Spring Harb Perspect Biol. 2016;8(11):a019463. doi: 10.1101/cshperspect.a019463.
68. Miller HA, Dean ES, Pletcher SD, Leiser SF. Cell non-autonomous regulation of health and longevity. Elife. 2020;9:e62659. doi: 10.7554/eLife.62659.
69. Hirata T, Arai Y, Yuasa S, Abe Y, Takayama M, Sasaki T, et al. Associations of cardiovascular biomarkers and plasma albumin with exceptional survival to the highest ages. Nat Commun. 2020;11(1):3820. doi: 10.1038/s41467-020-17636-0.
70. Mogilenko DA, Shpynov O, Andhey PS, Arthur L, Swain A, Esaulova E, et al. Comprehensive profiling of an aging immune system reveals clonal GZMK+CD8+T cells as conserved hallmark of inflammaging. Immunity. 2021;54(1):99-115.e12. doi: 10.1016/j.immuni.2020.11.005.
71. Carrasco E, Gómez de Las Heras MM, Gabandé-Rodríguez E, Desdín-Micó G, Aranda JF, Mittelbrunn M. The role of T cells in age-related diseases. Nat Rev Immunol. 2022;22(2):97-111. doi: 10.1038/s41577-021-00557-4.
72. Zmora N, Soffer E, Elinav E. Transforming medicine with the microbiome. Sci Transl Med. 2019;11(477):eaaw1815. doi: 10.1126/scitranslmed.aaw1815.