



Molecular drivers of ageing and emerging longevity therapies

Magaa Lakshmi Dhinakaran^{1†} , Sohnnakshee Murugesu^{1†} , Dinesh Kumar Srinivasan^{2*} 

¹School of Life Sciences, Management Development Institute of Singapore, Singapore 148951, Singapore

²Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117594, Singapore

[†]These authors contributed equally to this work.

***Correspondence:** Dinesh Kumar Srinivasan, Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, MD10, 4 Medical Drive, Singapore 117594, Singapore. dineshkumar@nus.edu.sg

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Abstract

Ageing is a gradual, multifactorial process that leads to the deterioration of physical and mental health, increasing the risk of disease and eventually death. Indicators of ageing manifest at the molecular level, including genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, and dysregulation of key signalling pathways such as the mechanistic target of rapamycin (mTOR) and insulin signalling. These molecular hallmarks of ageing are interconnected, amplifying one another over time. The resulting cellular stress triggers apoptosis or drives cells into a pathological state known as cellular senescence, in which they secrete inflammatory, pro-ageing factors. Consequently, there is a progressive decline in tissue function and regenerative capacity, accompanied by atrophy and stem cell exhaustion under a chronically inflamed microenvironment. Although functional decline with age is irreversible, research indicates it can be delayed. In this review, we discuss the hallmarks of ageing, conventional pharmacological interventions with demonstrated anti-ageing effects in cellular and animal models, and emerging therapeutic strategies being explored as ageing becomes increasingly recognized as a major risk factor for disease development.

Keywords

ageing, inflammation, senescence, hallmarks of ageing, therapeutic strategies

Introduction

The world is confronted with an ageing population on an unprecedented scale. Global life expectancy has increased by approximately 58% from 1950 to 2025 and continues to rise [1]. In contrast, global fertility rates have declined sharply, from 4.9 children per woman in 1950 to 2.3 in 2021 [2, 3]. This combination of longer life expectancy and a decreasing birth rate has produced a demographic shift toward older populations. Projections suggest that the population aged over 80 will triple, and those over 65 will double within the next 30 years [4]. This demographic transition presents major challenges. Ageing is accompanied by a rising prevalence of chronic diseases and disabilities, contributing to escalating healthcare costs

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worldwide. Meeting this demand requires robust, integrated healthcare systems capable of managing both acute and chronic age-related conditions [1, 5]. Non-communicable diseases such as cardiovascular and neurodegenerative disorders now account for nearly one-quarter of the global healthcare burden among those over 60 [6, 7]. Consequently, global healthcare spending is projected to reach 3.5 trillion USD this year, with an annual growth rate of at least 10% [8, 9].

Beyond healthcare, ageing has profound socio-economic consequences. As the share of working-age adults declines, labour shortages, slower economic growth, and rising dependency ratios place additional fiscal and social strain on families and governments [4, 10]. Retirees face increasing medical costs paired with reduced income, forcing both individuals and economies to allocate more resources toward sustaining older populations [11]. This pressure underscores an urgent need for advances in anti-ageing and longevity research. With growing scientific insight and medical innovation, ageing is being studied as a multifactorial biological process influenced by genetic, cellular, and environmental mechanisms. This review explores current understanding of these mechanisms and highlights both established and emerging therapeutic approaches aimed at delaying this inevitable process.

Key biological hallmarks of ageing

Genomic instability

Genomic instability refers to the accumulation of somatic mutations within the genome, which increases in frequency with age. These mutations include point mutations, deletions, chromosomal translocations, and DNA strand breaks. They can arise from endogenous sources, such as reactive oxygen species (ROS) generated during metabolism, or from exogenous sources, such as ultraviolet (UV) radiation. In normal cells, proteins such as DNA polymerases, glycosylases, nucleases, ligases, and protein complexes involved in DNA repair pathways, including base excision repair (BER) and nucleotide excision repair (NER), maintain genomic integrity [12]. As organisms age, the efficiency of DNA repair mechanisms declines due to downregulation of genes encoding these proteins, leading to the accumulation of unrepaired DNA damage in the form of mutations [6, 13]. Over time, when genetic damage reaches harmful levels, the cell cycle is halted, and apoptosis or cellular senescence is triggered [14].

Telomere attrition

Telomeres are protein–DNA structures located at the ends of linear chromosomes that act as protective caps, preventing chromosomal degradation and preserving genomic stability [15]. These repetitive non-coding sequences protect essential DNA from erosion during each round of replication, thereby addressing the end-replication problem [16]. Telomere attrition refers to the progressive shortening of telomeres over time due to both cell division and damage. The telomeric repeat sequence ‘TTAGGG’ is guanine-rich and particularly vulnerable to oxidative stress, especially from ROS [16, 17]. Oxidative damage accelerates telomere shortening beyond that caused by replication alone, and with age, cells exhibit a reduced capacity to counteract oxidative damage [18]. When telomere length reaches a critical threshold, cells undergo cell cycle arrest and are driven into cellular senescence or apoptosis [19].

Epigenetic alterations

Epigenetic alterations are heritable changes in gene activity that occur without modification of the underlying DNA sequence [6]. With age, four major types of epigenetic changes are typically observed: alterations in DNA methylation, histone protein dysregulation, non-coding RNA dysregulation, and changes in chromatin remodelling [20]. Ageing is associated with global hypomethylation, especially in repetitive regions, which can inappropriately expose normally silenced DNA to transcriptional activity and lead to aberrant gene expression. Conversely, hypermethylation may occur at promoters of protective genes, such as tumour suppressor genes, silencing their expression and reducing the cell’s capacity to prevent malignant transformation, thereby compromising genomic integrity [6].

Histone proteins, which regulate chromatin compaction and thereby control access to DNA, also undergo age-associated changes in abundance and structure. These changes can inappropriately activate normally silenced genes, such as oncogenes, or repress genes essential for genome maintenance and repair. Histone marks are crucial for recruiting DNA repair factors, and their dysregulation leads to impaired DNA repair [21]. Similarly, age-related dysregulation of non-coding RNAs, including microRNAs and long non-coding RNAs, disrupts normal post-transcriptional and transcriptional gene regulation, contributing to loss of homeostasis [22]. In addition, ageing is characterized by loss of constitutive heterochromatin and disruption of higher-order chromatin organization, due in part to altered chromatin-remodelling complexes, reduced sirtuin activity, and damage to the nuclear lamina [6]. These epigenetic and structural alterations, combined with genomic instability and inefficient repair, promote cellular stress and lead to apoptosis or cellular senescence, thereby contributing to ageing.

Loss of proteostasis

Proteostasis refers to the dynamic balance of protein synthesis, folding, quality control, and degradation necessary to maintain a functional proteome. With ageing, this balance becomes disrupted, leading to an accumulation of misfolded and aggregated proteins [23, 24]. Impaired protein degradation and reduced chaperone activity result in fewer correctly folded, functional proteins, while defects in protein trafficking further compromise cellular function. Aggregated proteins exert proteotoxic stress, interfering with normal cell processes and triggering cellular stress responses that may lead to apoptosis or cellular senescence. The accumulation of senescent cells and cell death associated with loss of proteostasis has been implicated in several age-related neurodegenerative disorders [25].

Mitochondrial dysfunction

A decline in mitochondrial function and number is a common feature of ageing [26]. Mitochondria primarily generate adenosine triphosphate (ATP) through oxidative phosphorylation, which depends on the electron transport chain (ETC), comprising respiratory complexes I–IV and ATP synthase [27]. Ageing is associated with reduced activity of complexes I and IV, whereas changes in complexes II and III are generally less pronounced [28]. Reduced ETC efficiency promotes electron leakage, increasing ROS production and further damaging cellular components [29].

Mitochondrial DNA (mtDNA) accumulates mutations with age, similar to nuclear DNA, which further impairs mitochondrial function and exacerbates ROS generation. mtDNA is particularly vulnerable because it lacks protective histones and relies mainly on BER, with limited capacity for other repair pathways such as NER and mismatch repair (MMR) [29]. As a result, mtDNA damage accumulates, worsening mitochondrial dysfunction and contributing to cellular stress. In healthy cells, mitochondria undergo continuous fission and fusion to maintain quality control and enable the segregation or removal of damaged components through mitophagy [30]. With age, the expression of fission and fusion proteins becomes dysregulated, leading to either excessively fragmented or hyperfused mitochondria, both of which are functionally compromised [27, 30].

Mitochondrial dysfunction increases ROS production, amplifying macromolecular damage, while reduced oxidative phosphorylation leads to diminished ATP levels and an energy deficit that undermines cellular maintenance and repair, thereby heightening cellular stress [27]. The mitochondrial unfolded protein response (mtUPR), a stress pathway that maintains mitochondrial protein homeostasis, also declines with age. Under proteotoxic stress, the mtUPR activates transcription factors that translocate to the nucleus and upregulate genes encoding mitochondrial chaperones, co-chaperones, and proteases, promoting clearance of misfolded proteins and restoration of proteostasis [27, 31]. With ageing, reduced mtUPR efficiency impairs the removal of damaged proteins, destabilizes the ETC, increases ROS production, and promotes further mtDNA damage, ultimately driving mitochondrial dysfunction and, downstream, cellular senescence or apoptosis [31].

mTOR dysregulation

The mechanistic target of rapamycin (mTOR) is a serine/threonine protein kinase that regulates cellular metabolism, growth, survival, autophagy, and immune responses [32]. mTOR functions in two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [32, 33]. mTORC1 primarily senses nutrient and growth factor availability to regulate protein synthesis and metabolism, whereas mTORC2 is more closely associated with cell survival, proliferation, and cytoskeletal organization [34]. Together, these complexes help maintain the balance between anabolism and catabolism in response to cellular conditions [33].

With advancing age, mTOR activity is often found to be chronically elevated, promoting anabolic processes while inhibiting catabolic pathways such as autophagy, leading to loss of metabolic homeostasis [34, 35]. Although the precise mechanisms by which mTOR contributes to ageing are still being elucidated, hyperactivation of this pathway is known to increase oxidative and proteotoxic stress, reduce cellular stress resistance, and impair clearance of damaged macromolecules. These changes collectively accelerate functional decline and promote the onset of age-related pathologies. While the exact mechanism of action of this complex is still not fully understood, it is known to increase oxidative and proteotoxic stress within cells, decrease autophagy, cause mitochondrial dysfunction, and dampen the sensitivity and feedback control of nutrient-sensing pathways, thereby impairing the body's ability to adapt to nutrient scarcity and hastening cellular senescence [34, 36]. The insulin/insulin-like growth factor (IGF)-1 signalling (IIS) pathway also activates mTOR, which can accelerate ageing when excessively stimulated and increases oxidative damage and ROS generation due to impaired mitochondrial activity [6].

Insulin sensitivity

Research shows that the body's ability to respond to insulin deteriorates with age, although the precise pathophysiological mechanisms underlying this change remain unclear [37, 38]. Reduced insulin sensitivity results in hyperinsulinaemia, which has multiple downstream repercussions in cells and may be related to increased body fat and decreased lean mass [39–41]. Additionally, nutrient signalling through the IIS pathway, mediated by pancreatic beta cells during fasting–feeding cycles, is one of the primary pathways influencing ageing and becomes dysregulated with age [39, 42]. Insulin is secreted in response to glucose and promotes anabolic processes, while IGF-1 is a growth factor stimulated by hormones to support cell division and proliferation [43]. Under appropriate regulation, these mechanisms are beneficial, but with age they can become dysregulated and promote excessive anabolism, disrupting metabolic homeostasis and accelerating ageing [43, 44]. Specifically, the IIS pathway can drive ageing by suppressing the transcription factor forkhead box O (FOXO), which is essential for maintaining cellular quality control, particularly under stress and nutrient deprivation [44–46].

Interconnectedness and impact of hallmarks

Among the nine hallmarks of ageing originally described by López-Otín et al. [6] (2013), which more recent work has expanded to fourteen, this review focuses on seven that most directly align with the therapeutic pathways discussed, to maintain a relevant scope [47]. These molecular indicators of ageing are not independent phenomena but are interconnected through overlapping pathways that exacerbate one another. Progression of dysfunction in one hallmark can precipitate decline in others. For example, epigenetic alterations can promote genomic instability and influence downstream factors such as telomere attrition and loss of proteostasis [6, 48]. Similarly, overactivation of mTOR increases the likelihood of mitochondrial dysfunction and loss of proteostasis, thereby promoting cellular senescence and further accelerating ageing [49, 50].

Cellular senescence usually occurs when damaged or stressed cells permanently stop dividing. Senescent cells secrete a collection of factors termed the senescence-associated secretory phenotype (SASP), which drives chronic inflammation and tissue damage [51]. The SASP includes pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, IL-1 β , tumour necrosis factor-alpha (TNF- α), monocyte chemoattractant protein-1 (MCP-1), growth factors, and matrix metalloproteinases (MMPs), which are

persistently secreted, as described by Coppé et al. [52]. These factors recruit monocytes, macrophages, neutrophils, and other immune cells, leading to chronic immune activation, and can also induce senescence in neighbouring cells, amplifying the impact of ageing [52]. MMPs contribute to the degradation of the extracellular matrix, weakening tissue structural integrity [52]. Additionally, senescent cells activate senescent cell anti-apoptotic pathways (SCAPs), enabling them to resist apoptosis and persist, thereby amplifying their detrimental effects [53, 54]. When cells become senescent or undergo apoptosis in response to damage, the pool of functional cells within tissues declines. This loss is particularly critical in muscle, immune, and brain tissues, which already exhibit reduced regenerative potential with age. Senescence and apoptosis also deplete stem cell pools, as stem cells undergo repeated divisions to replace lost cells and eventually experience exhaustion, losing self-renewal and differentiation capacity despite the presence of telomerase [6, 55]. This stem cell exhaustion leads to impaired regeneration and tissue repair [56] (Figure 1).

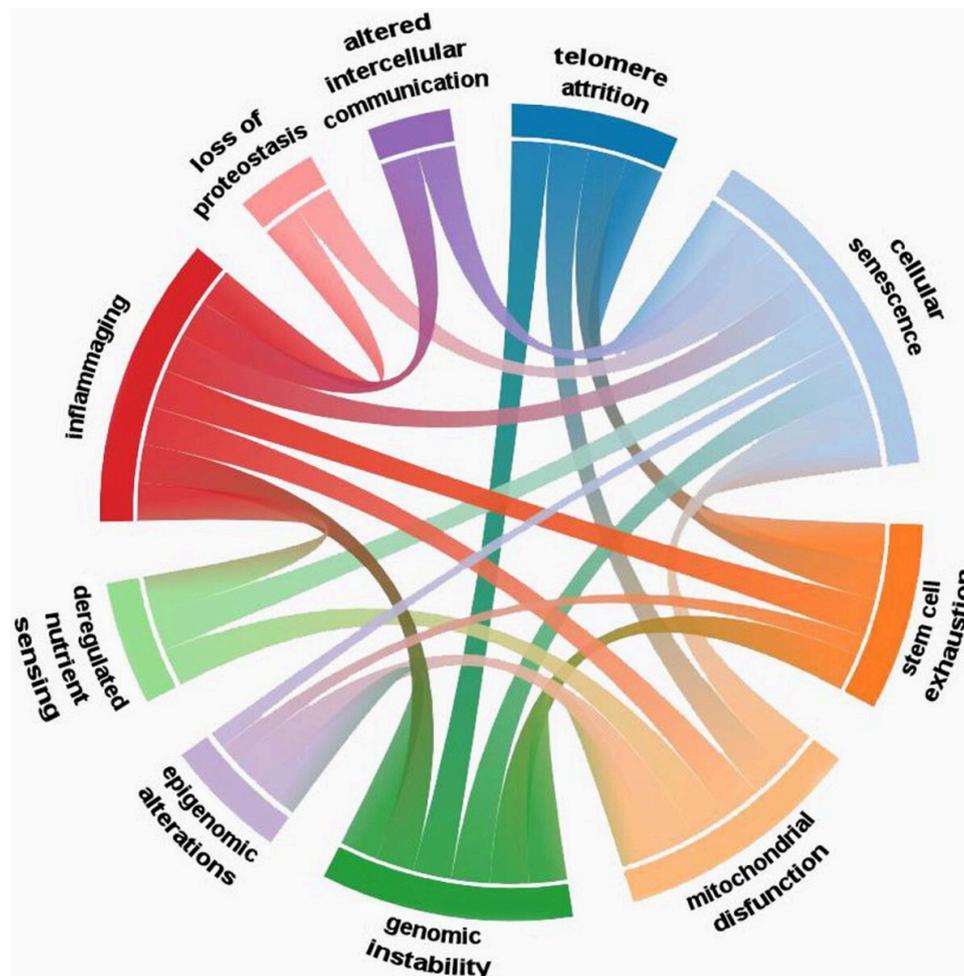


Figure 1. Interrelations between the hallmarks of aging. Reprinted from [56]. © 2023 The Authors. Licensed under CC-BY 4.0.

Anti-ageing strategies

Although no drugs have been officially approved specifically for anti-ageing treatment, several therapies have attracted considerable interest for their mechanisms that promote anti-ageing and for their observed anti-ageing effects in individuals receiving them for other medical conditions.

Metformin

Metformin is a small molecule widely noted for its potential anti-ageing effects in patients prescribed this drug as a first-line treatment for type II diabetes [57]. Multiple mechanisms of action have been proposed

for metformin, many of which converge on improved geroprotection [58]. Primarily, metformin lowers blood glucose and lipid levels by activating AMP-activated protein kinase (AMPK), a central energy sensor. This activation promotes increased glucose uptake by myocytes, downregulates gluconeogenesis in hepatocytes, improves insulin sensitivity in both myocytes and hepatocytes, suppresses the expression of lipogenic enzymes, enhances fatty acid oxidation, and reduces serum triglyceride and low-density lipoprotein (LDL) levels [58–61]. These effects help maintain glycaemic control and confer cardioprotective benefits [62].

On a broader scale, AMPK activation indirectly suppresses mTOR signalling and shifts cellular metabolism away from excessive anabolism towards more catabolic and stress-resistant states, thereby mitigating pro-ageing mTOR activity [63, 64]. Metformin also reduces ROS production by partially inhibiting mitochondrial complex I and promotes mitochondrial biogenesis through the AMPK–peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) axis [65]. In addition, it exerts anti-inflammatory effects by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signalling and downregulating pro-inflammatory cytokines such as IL-6 and TNF- α , thereby attenuating the SASP [65]. These actions contribute to improved systemic homeostasis, reduced chronic inflammation, and preservation of genomic and cellular integrity. Furthermore, metformin influences epigenetic regulation by modulating DNA methylation and microRNA expression patterns associated with longevity [66]. Collectively, these multifaceted effects position metformin as a promising gerotherapeutic agent [67, 68]. Although metformin is not currently prescribed solely as an anti-ageing therapy, the landmark Targeting Ageing with Metformin (TAME) trial is in the preparatory phase and is designed to test whether metformin can delay the onset of multiple age-related diseases simultaneously [69] (Figure 2).

Dasatinib and quercetin

Dasatinib and quercetin are agents that have received increasing attention in anti-ageing research. Dasatinib was initially developed as an anticancer drug but was later found to be efficacious when combined with quercetin, forming a potentially powerful senolytic regimen for age-related disorders [70–72]. The dasatinib–quercetin (DQ) combination can selectively eliminate senescent cells, which accumulate with age and contribute to chronic inflammation and tissue dysfunction [73]. Dasatinib inhibits multiple tyrosine kinases that are often overexpressed in senescent cells, selectively targeting senescent preadipocytes, haematopoietic progenitors, chondrogenic stem cells, subsets of fibroblasts, and endothelial cells [70, 71, 74, 75]. It also interferes with SCAPs and induces apoptosis in these pathogenic cells [76]. Quercetin, a flavonoid, helps reduce fat accumulation and senescence markers [75].

Several translational studies have shown that DQ treatment significantly reduces senescent cell burden and improves various health parameters, including bone health, metabolic function, inflammation, and cardiac performance [75, 77, 78]. DQ has also shown promise in aesthetic applications, such as skin rejuvenation, by eliminating senescent dermal fibroblasts and enhancing collagen density [79]. Currently, dasatinib is clinically prescribed for certain forms of leukaemia, whereas quercetin is available over the counter mainly for its antioxidant and anti-inflammatory properties. This combination is not yet approved by the U.S. Food and Drug Administration (FDA) for any indication [79, 80]. However, multiple clinical trials are underway to evaluate its potential to mitigate ageing, including studies on reversing osteoporosis in elderly women, improving physical function in individuals with idiopathic pulmonary fibrosis, enhancing gait and cognitive performance in older adults, slowing the progression of Alzheimer's disease, and assessing its impact on biological ageing [81–83].

Monoclonal antibodies

Monoclonal antibodies offer high specificity in targeting ageing-associated pro-inflammatory cytokines such as IL-6 and were initially developed for conditions like autoimmune diseases and cancer [84–86]. More recently, they have been explored as potential agents to reduce chronic low-grade inflammation in ageing-associated disorders [87–89]. IL-6, a widely produced cytokine, exerts pleiotropic effects in tissues surrounding senescent cells [90]. It is a major driver of inflammation and participates in a positive feedback

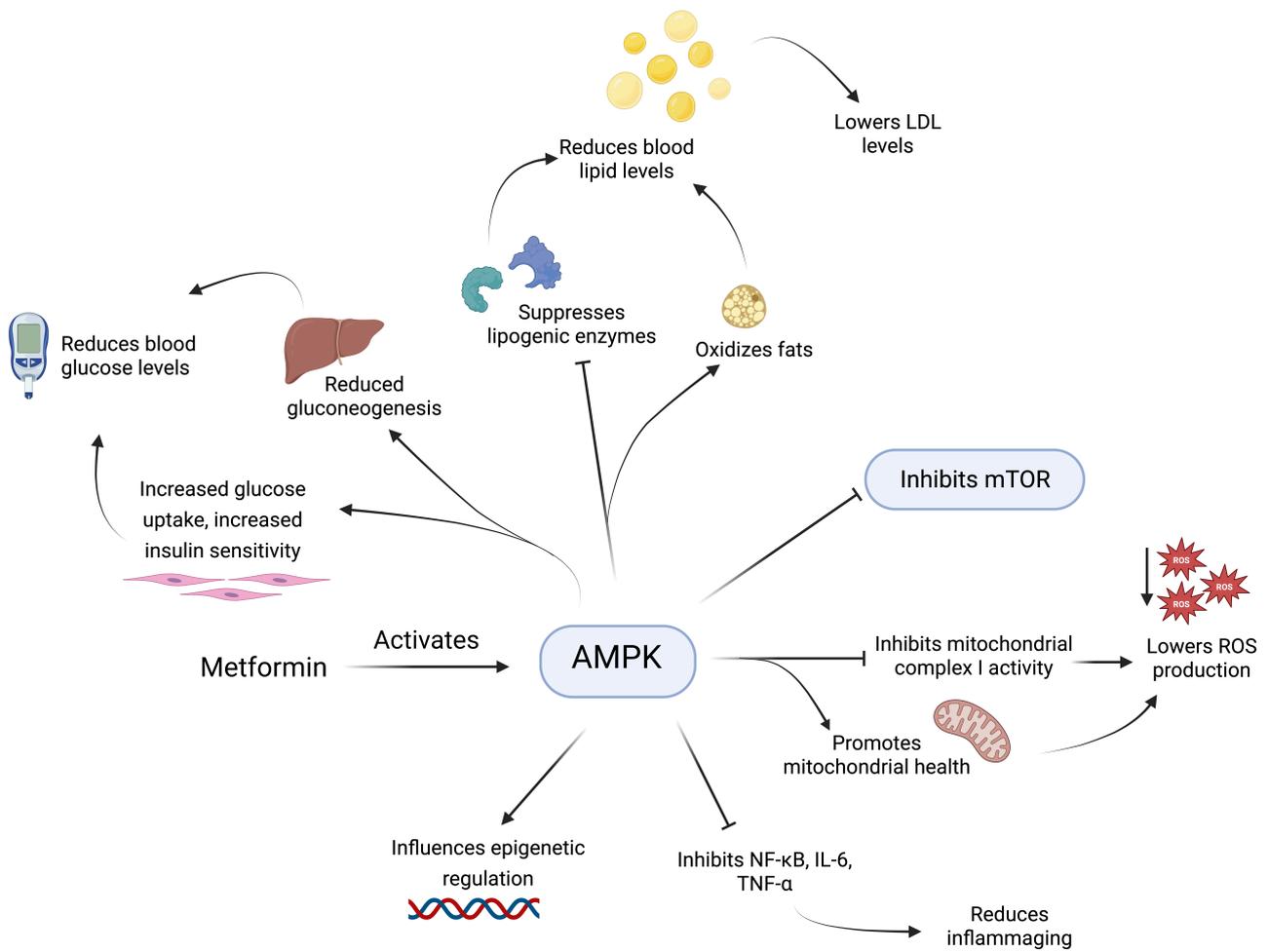


Figure 2. Mode of action of metformin via AMPK activation. Metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK), which leads to enhanced glucose uptake and reduced hepatic gluconeogenesis, causing reduced blood glucose levels, suppresses lipogenic enzymes and oxidizes fats, reducing blood lipid levels, inhibits mechanistic target of rapamycin (mTOR) signalling, improves mitochondrial health and inhibits mitochondrial complex I activity, effectively reducing ROS production, inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) which reduces inflammaging, and allows for increased epigenetic regulation. LDL: low-density lipoprotein; ROS: reactive oxygen species. Created in BioRender. Dhinakaran, M. (2026) <https://BioRender.com/gycdzpa>.

loop with mitochondrial dysfunction [86]. Moreover, elevated IL-6 has been implicated in skewing haematopoietic stem cells towards myeloid differentiation, increasing mutational risk, and adversely affecting cardiac tissue [91, 92].

By suppressing IL-6 signalling, these adverse effects may be mitigated and the pace of ageing-related decline potentially reduced [86]. By neutralising specific SASP components, monoclonal antibody therapies aim to restore tissue homeostasis and function. The humanised monoclonal antibody tocilizumab and the fully human antibody sarilumab bind to IL-6 receptors and prevent IL-6 from engaging them, thereby blocking downstream signalling cascades initiated by this cytokine [93, 94]. Inhibiting IL-6-mediated pathways has shown potential to improve tissue integrity and function [86, 91]. Ongoing clinical trials are investigating whether IL-6 inhibition can slow aspects of biological ageing and improve outcomes in patients with inflammatory disorders such as rheumatoid arthritis, polymyalgia rheumatica, and chronic kidney disease [95].

Stem cell regenerative therapies

Stem cell-based therapies seek to replenish or rejuvenate aged tissues. Mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) show considerable promise for treating degenerative conditions of the brain, heart, and musculoskeletal system [96–98]. These cells can repair age-related tissue damage, modulate immune responses, and differentiate into multiple lineages, making them attractive candidates for regenerative applications [96–98]. Ageing, however, impairs the regenerative capacity of endogenous

stem cells through mechanisms such as accumulated DNA damage, epigenetic alterations, mitochondrial dysfunction, and telomere shortening, underscoring the need for strategies to enhance stem cell efficacy [98].

At present, stem cell therapy is approved for certain indications, including graft-versus-host disease and specific haematological and immune disorders [99, 100]. Numerous clinical trials are ongoing to evaluate its utility in alleviating ageing-related degenerative conditions, such as Parkinson's disease, osteoporosis, and ischaemic heart disease [74, 101, 102].

Emerging therapeutic strategies

Beyond therapies that have shown benefit in other diseases and may be repurposed to slow ageing, several novel approaches are emerging as important areas of investigation. Although still largely experimental, these strategies are underpinned by a strong mechanistic rationale.

Gene editing methods: CRISPR-CRISPR-associated protein 9 (Cas9)

Clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 is a versatile genome-editing platform that enables precise modification of DNA to silence or alter specific genes [103, 104]. Guided by a 20-nucleotide single-guide RNA (sgRNA), Cas9 introduces double-strand breaks that are repaired by cellular DNA repair pathways, typically non-homologous end joining (NHEJ), resulting in gene knockouts, or by homology-directed repair (HDR) when a repair template is provided [103, 104] (Figure 3). This technology has markedly shortened the time required to generate genetically engineered mice, from over a year to a matter of months [105, 106].

In mouse zygote microinjection or electroporation experiments, high-efficiency editing has been reported, with up to 100% NHEJ and 27% HDR in ten-eleven translocation methylcytosine dioxygenase 2 (Tet2)-targeted embryos [107]. These studies demonstrate that CRISPR-Cas9 can efficiently produce knockouts, knock-ins, large deletions, conditional alleles, and multiplexed gene alterations in a single step [105, 108, 109]. Despite concerns regarding large deletions at target sites, mosaicism, and off-target effects, the speed, scalability, and cost-effectiveness of CRISPR-Cas9 have made it indispensable for functional genomics, disease modelling, and preclinical therapeutic ageing research [105, 108]. For example, CRISPR-Cas9 has been used in mouse models to reduce senescence in hepatocytes and attenuate liver ageing by inactivating the *KAT7* gene, which codes for a histone acetyltransferase, thereby extending lifespan [110]. In another study, epigenetic reactivation of telomerase reverse transcriptase (TERT) using CRISPR-Cas9 extended the lifespan of T cells in vitro and delayed their senescence [111]. With a growing number of studies applying CRISPR-Cas9 to interrogate molecular drivers of ageing, CRISPR-based rejuvenation strategies are now actively being explored.

Sirtuin 6 upregulation

Sirtuin 6 (SIRT6), with its first functional characterisation in 2006, has gained increasing attention as a key molecular target in ageing research due to its multifaceted roles, which have been shown to extend lifespan in preclinical models [112, 113]. SIRT6 is a nicotinamide adenine dinucleotide (NAD⁺)-dependent histone deacetylase involved in critical metabolic signalling pathways. Quercetin derivatives have also been shown to modulate SIRT6 activity, with some acting as activators [114]. SIRT6 promotes longevity by enhancing DNA repair, maintaining chromosomal integrity, regulating energy metabolism, and suppressing SASP production [115–119].

SIRT6 protects telomeres by deacetylating histone H3 in telomeric regions, compacting chromatin to shield DNA from damage [115]. It also promotes BER, NHEJ, and homologous recombination (HR) by activating BER enzymes and poly(ADP-ribose) polymerase 1 (PARP1), thereby enhancing cellular resistance to DNA damage and supporting longevity [116, 117]. This protective effect was demonstrated in a study showing SIRT6-mediated repair of UV-induced DNA damage [116]. In metabolism, SIRT6 represses glycolysis through histone deacetylation, redirecting glucose towards efficient mitochondrial respiration [119]. SIRT6-deficient mice exhibit increased glycolytic flux, leading to dysregulated glucose uptake and

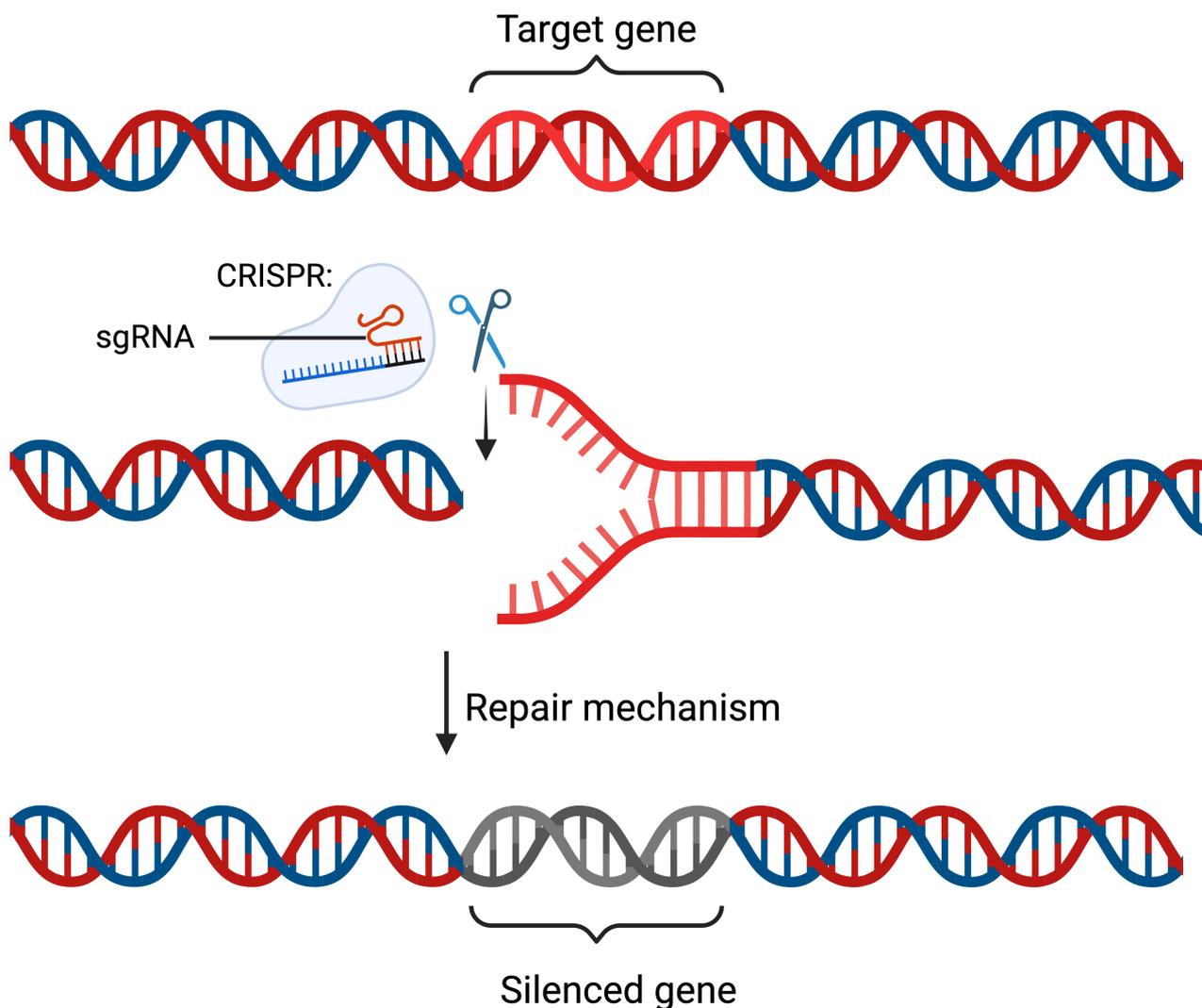


Figure 3. CRISPR-Cas9 mediated gene silencing mechanism. The clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9 (CRISPR-Cas9) mechanism uses sgRNA to direct the Cas9 nuclease to a specific DNA sequence, where it introduces a double-strand break that disrupts gene expression, leading to the silencing of a gene. sgRNA: single-guide RNA. Created in BioRender. Dhinakaran, M. (2026) <https://BioRender.com/dqtxiea>.

hypoglycaemia [119]. SIRT6 also inhibits gluconeogenesis, modulates β -cell insulin secretion, and improves insulin sensitivity [119]. In lipid metabolism, SIRT6 suppresses proprotein convertase subtilisin/kexin type 9 (*PCSK9*) expression via histone acetylation, preserving LDL receptor levels and reducing cardiovascular risk [120, 121].

Furthermore, SIRT6 attenuates chronic inflammation by deacetylating histones at NF- κ B gene promoters, suppressing inflammatory cytokine production [122]. It interacts with nuclear factor erythroid 2-related factor 2 (NRF2) to upregulate antioxidant genes, protecting against ROS [123]. Early human clinical trials are now underway to evaluate SIRT6 upregulation using modulators and activators, with initial data indicating promising safety and effective target engagement [48, 82, 124].

Coatomer protein complex I pathway and N-myristoyltransferase inhibitors

A 2023 University College London study identified the coatomer protein complex I (COPI) pathway as a novel target for senescent cell elimination using RNA interference (RNAi) screens [125]. In normal cells, COPI mediates retrograde vesicle transport between the endoplasmic reticulum and Golgi apparatus, involving cargo selection, ADP-ribosylation factor 1 (ARF1) activation, coat assembly, vesicle budding and scission, uncoating, targeting, and fusion [126]. In senescent cells, ARF1 activity is upregulated [127]. ARF1 requires N-terminal myristoylation for activation; N-myristoyltransferase inhibitors (NMTi) suppress this, thereby repressing COPI function [126].

Pharmacological or genetic COPI suppression induces Golgi apparatus dispersal, impaired autophagy, and apoptosis via the unfolded protein response. While NMTi affect both normal and senescent cells, Golgi apparatus disruption and reduced secretion occur selectively in the latter [125]. This inhibits SASP factors trafficking (e.g., IL-6, IL-8), preventing secretion despite ongoing translation [125]. Although target cells remain senescent, this approach reduces inflammation, limits paracrine senescence spread, protects stem cells, and slows tissue degeneration [126]. Preclinical data are promising, and clinical trials may follow soon [128].

RNAi for senescence-associated targets

RNAi uses short hairpin RNA (shRNA) or small interfering RNA (siRNA) to silence genes by degrading target messenger RNA (mRNA) [129]. Double-stranded RNA is processed by Dicer into siRNA, which loads into the RNA-induced silencing complex (RISC). RISC binds complementary mRNA, cleaving it for degradation [130, 131]. In anti-ageing research, RNAi targets senescent cells or SASP to restore tissue function [132, 133].

Clinical trials are testing RNAi for age-related conditions. For age-related macular degeneration (AMD), targeting myeloid differentiation primary response 88 (MYD88) mRNA reduces inflammation and tissue damage [134, 135]. In amyloidosis, a precursor to atherosclerosis and dementia, transthyretin (TTR) mRNA targeting reduces amyloid deposition [136–138]. For fibrosis, common in the elderly and impairing organ repair, perilipin 2 (PLIN2) targeting alleviates liver fibrosis [139]. These applications highlight RNAi's potential in age-related diseases.

Future trends and challenges

Therapeutic strategies, both repurposed and emerging, show strong preclinical promise. However, clinical trials for ageing interventions face challenges, particularly in identifying validated biomarkers as surrogate endpoints [140]. Epigenetic clocks, telomere length, and inflammatory profiles are common, but their predictive value requires further validation [140, 141]. Composite biomarkers may offer greater accuracy, though standardised frameworks are lacking [142, 143]. Regulatory hurdles persist, as agencies like the FDA and European Medicines Agency (EMA) prioritise disease-specific approvals over broad geroprotection [132, 133].

Ethical concerns centre on balancing lifespan extension with healthspan. Interventions must enhance functional wellbeing, not just longevity, to avoid prolonged frailty [144]. Access inequities loom large, with ageing research often excluding disadvantaged groups, exacerbating disparities [145, 146]. Low- and middle-income countries face barriers like poor infrastructure and financial constraints [147]. Advanced therapies risk creating a “longevity divide” favouring the affluent population [148]. Solutions include global infrastructure investment, and policies ensuring affordability and equity.

Conclusions

Ageing remains an inevitable biological process that affects every individual through interconnected molecular hallmarks, including genomic instability, telomere attrition, epigenetic alterations, proteostasis loss, mitochondrial dysfunction, mTOR dysregulation, and cellular senescence. This review has analysed these hallmarks and highlighted how repurposed therapies—such as metformin, DQ combinations, monoclonal antibodies, and stem cell interventions—demonstrate translational promise by targeting these pathways to improve metabolic homeostasis, reduce inflammation, and enhance cellular repair. Emerging strategies, including SIRT6 upregulation, COPI pathway inhibition, RNAi therapeutics, and CRISPR-Cas9 gene editing, offer innovative opportunities to address ageing at its biological roots, with preclinical data showing lifespan extension and tissue rejuvenation in model organisms.

Despite these advances, significant challenges persist. Reliable biomarkers, such as epigenetic clocks and composite inflammatory profiles, require further validation for use as surrogate endpoints in clinical trials. Regulatory frameworks from agencies like the FDA and EMA prioritise disease-specific approvals,

complicating direct testing of geroprotective agents. Ethical considerations are paramount, emphasising the need to extend healthspan alongside lifespan to avoid prolonged frailty, while addressing access inequities that could create a “longevity divide” favouring affluent populations.

Future progress demands multidisciplinary integration: rigorous mechanistic studies, inclusive clinical trials, standardised biomarker frameworks, and policy reforms for equitable access. By combining lifestyle interventions with pharmacological and biotechnological innovations, anti-ageing research holds transformative potential to compress morbidity, enhance quality of life, and extend human longevity in the decades ahead.

Abbreviations

AMPK: AMP-activated protein kinase

ARF1: ADP-ribosylation factor 1

ATP: adenosine triphosphate

BER: base excision repair

Cas9: clustered regularly interspaced short palindromic repeats-associated protein 9

COPI: coatamer protein complex I

CRISPR: clustered regularly interspaced short palindromic repeats

DQ: dasatinib–quercetin

EMA: European Medicines Agency

ETC: electron transport chain

FDA: Food and Drug Administration

HDR: homology-directed repair

IGF: insulin-like growth factor

IIS: insulin/insulin-like growth factor-1 signalling

IL: interleukin

LDL: low-density lipoprotein

MMPs: matrix metalloproteinases

mRNA: messenger RNA

mtDNA: mitochondrial DNA

mTOR: mechanistic target of rapamycin

mTORC1: mechanistic target of rapamycin complex 1

mTORC2: mechanistic target of rapamycin complex 2

mtUPR: mitochondrial unfolded protein response

NER: nucleotide excision repair

NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells

NHEJ: non-homologous end joining

NMTi: N-myristoyltransferase inhibitors

RISC: RNA-induced silencing complex

RNAi: RNA interference

ROS: reactive oxygen species

SASP: senescence-associated secretory phenotype

SCAPs: senescent cell anti-apoptotic pathways

siRNA: small interfering RNA

SIRT6: sirtuin 6

TNF- α : tumour necrosis factor-alpha

UV: ultraviolet

Declarations

Author contributions

MLD: Investigation, Writing—original draft, Writing—review & editing, Visualization. SM: Investigation, Writing—original draft, Writing—review & editing, Visualization. DKS: Conceptualization, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

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References

1. Dattani S, Rodés-Guirao L, Ritchie H, Ortiz-Ospina E, Roser M. Life Expectancy [Internet]. [cited 2025 Aug 11]. Available from: <https://ourworldindata.org/life-expectancy>
2. GBD 2021 Fertility and Forecasting Collaborators. Global fertility in 204 countries and territories, 1950-2021, with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403:2057–99. [DOI] [PubMed] [PMC]
3. State of World Population 2023: 8 Billion Lives, Infinite Possibilities - The case for rights and choices [Internet]. reliefweb; c2026 [cited 2025 Jul 13]. Available from: <https://reliefweb.int/report/world/state-world-population-2023-8-billion-lives-infinite-possibilities-case-rights-and-choices-enarru>

4. World Population Prospects 2022: Summary of Results [Internet]. [cited 2025 Jul 13]. Available from: <https://www.un.org/development/desa/pd/content/World-Population-Prospects-2022>
5. Araujo de Carvalho I, Epping-Jordan J, Pot AM, Kelley E, Toro N, Thiyagarajan JA, et al. Organizing integrated health-care services to meet older people's needs. *Bull World Health Organ*. 2017;95:756–63. [DOI] [PubMed] [PMC]
6. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153:1194–217. [DOI] [PubMed] [PMC]
7. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. *Lancet*. 2015;385:549–62. [DOI] [PubMed]
8. McGough M, Telesford I, Winger A, Cotter L, Cox C. How much is health spending expected to grow? [Internet]. PETERSON-KFF Health System Tracker; 2026 [cited 2025 Jul 20]. Available from: <https://www.healthsystemtracker.org/chart-collection/how-much-is-health-spending-expected-to-grow/>
9. Global spending on health: Coping with the pandemic [Internet]. WHO; c2026 [cited 2025 Jul 25]. Available from: <https://www.who.int/publications/i/item/9789240086746>
10. Malki ST, Johansson P, Andersson G, Andréasson F, Mourad G. Caregiver burden, psychological well-being, and support needs among Swedish informal caregivers. *BMC Public Health*. 2025;25:867. [DOI] [PubMed] [PMC]
11. Kallestrup-Lamb M, Marin AOK, Menon S, Søggaard J. Aging populations and expenditures on health. *J Econ Ageing*. 2024;29:100518. [DOI]
12. Panier S, Wang S, Schumacher B. Genome Instability and DNA Repair in Somatic and Reproductive Aging. *Annu Rev Pathol*. 2024;19:261–90. [DOI] [PubMed]
13. Hoeijmakers JH. DNA damage, aging, and cancer. *N Engl J Med*. 2009;361:1475–85. [DOI] [PubMed]
14. Gorbunova V, Seluanov A, Mao Z, Hine C. Changes in DNA repair during aging. *Nucleic Acids Res*. 2007;35:7466–74. [DOI] [PubMed] [PMC]
15. d'Adda di Fagagna F. Living on a break: cellular senescence as a DNA-damage response. *Nat Rev Cancer*. 2008;8:512–22. [DOI] [PubMed]
16. Lee J, Pellegrini MV. *Biochemistry, Telomere And Telomerase*. Treasure Island (FL): StatPearls Publishing; 2025.
17. von Zglinicki T. Oxidative stress shortens telomeres. *Trends Biochem Sci*. 2002;27:339–44. [DOI] [PubMed]
18. d'Adda di Fagagna F, Reaper PM, Clay-Farrace L, Fiegler H, Carr P, Von Zglinicki T, et al. A DNA damage checkpoint response in telomere-initiated senescence. *Nature*. 2003;426:194–8. [DOI] [PubMed]
19. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol*. 2007;8:729–40. [DOI] [PubMed]
20. Tsurumi A, Li WX. Global heterochromatin loss: a unifying theory of aging? *Epigenetics*. 2012;7:680–8. [DOI] [PubMed] [PMC]
21. Booth LN, Brunet A. The Aging Epigenome. *Mol Cell*. 2016;62:728–44. [DOI] [PubMed] [PMC]
22. Maslov AY, Vijg J. Genome instability, cancer and aging. *Biochim Biophys Acta*. 2009;1790:963–9. [DOI] [PubMed] [PMC]
23. Hipp MS, Kasturi P, Hartl FU. The proteostasis network and its decline in ageing. *Nat Rev Mol Cell Biol*. 2019;20:421–35. [DOI] [PubMed]
24. Lim SM, Nahm M, Kim SH. Proteostasis and Ribostasis Impairment as Common Cell Death Mechanisms in Neurodegenerative Diseases. *J Clin Neurol*. 2023;19:101–14. [DOI] [PubMed] [PMC]
25. Meller A, Shalgi R. The aging proteostasis decline: From nematode to human. *Exp Cell Res*. 2021;399:112474. [DOI] [PubMed] [PMC]

26. Manczak M, Jung Y, Park BS, Partovi D, Reddy PH. Time-course of mitochondrial gene expressions in mice brains: implications for mitochondrial dysfunction, oxidative damage, and cytochrome c in aging. *J Neurochem*. 2005;92:494–504. [DOI] [PubMed]
27. Sun N, Youle RJ, Finkel T. The Mitochondrial Basis of Aging. *Mol Cell*. 2016;61:654–66. [DOI] [PubMed] [PMC]
28. Payne BA, Chinnery PF. Mitochondrial dysfunction in aging: Much progress but many unresolved questions. *Biochim Biophys Acta*. 2015;1847:1347–53. [DOI] [PubMed] [PMC]
29. Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature*. 2004;429:417–23. [DOI] [PubMed]
30. Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. *Science*. 2012;337:1062–5. [DOI] [PubMed] [PMC]
31. Fiorese CJ, Schulz AM, Lin YF, Rosin N, Pellegrino MW, Haynes CM. The Transcription Factor ATF5 Mediates a Mammalian Mitochondrial UPR. *Curr Biol*. 2016;26:2037–43. [DOI] [PubMed] [PMC]
32. Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, Raza AS, et al. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. *Signal Transduct Target Ther*. 2023;8:375. [DOI] [PubMed] [PMC]
33. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. *Cell*. 2017;168:960–76. [DOI] [PubMed] [PMC]
34. Xu S, Cai Y, Wei Y. mTOR Signaling from Cellular Senescence to Organismal Aging. *Aging Dis*. 2014;5:263–73. [DOI] [PubMed] [PMC]
35. Liu X, Guo B, Li Q, Nie J. mTOR in metabolic homeostasis and disease. *Exp Cell Res*. 2024;441:114173. [DOI] [PubMed]
36. Antikainen H, Driscoll M, Haspel G, Dobrowolski R. TOR-mediated regulation of metabolism in aging. *Aging Cell*. 2017;16:1219–33. [DOI] [PubMed] [PMC]
37. Kolb H, Kempf K, Martin S. Insulin and aging – a disappointing relationship. *Front Endocrinol (Lausanne)*. 2023;14:1261298. [DOI] [PubMed] [PMC]
38. Guo X, Asthana P, Gurung S, Zhang S, Wong SKK, Fallah S, et al. Regulation of age-associated insulin resistance by MT1-MMP-mediated cleavage of insulin receptor. *Nat Commun*. 2022;13:3749. [DOI] [PubMed] [PMC]
39. Lu M, Li C. Nutrient sensing in pancreatic islets: lessons from congenital hyperinsulinism and monogenic diabetes. *Ann N Y Acad Sci*. 2018;1411:65–82. [DOI] [PubMed] [PMC]
40. Lee CG, Boyko EJ, Strotmeyer ES, Lewis CE, Cawthon PM, Hoffman AR, et al.; Osteoporotic Fractures in Men Study Research Group. Association between insulin resistance and lean mass loss and fat mass gain in older men without diabetes mellitus. *J Am Geriatr Soc*. 2011;59:1217–24. [DOI] [PubMed] [PMC]
41. Tessari P. Role of insulin in age-related changes in macronutrient metabolism. *Eur J Clin Nutr*. 2000;54:S126–30. [DOI] [PubMed]
42. Johnson SC. Nutrient Sensing, Signaling and Ageing: The Role of IGF-1 and mTOR in Ageing and Age-Related Disease. *Subcell Biochem*. 2018;90:49–97. [DOI] [PubMed]
43. Salminen A, Kaarniranta K, Kauppinen A. Insulin/IGF-1 signaling promotes immunosuppression via the STAT3 pathway: impact on the aging process and age-related diseases. *Inflamm Res*. 2021;70:1043–61. [DOI] [PubMed] [PMC]
44. Li WJ, Wang CW, Tao L, Yan YH, Zhang MJ, Liu ZX, et al. Insulin signaling regulates longevity through protein phosphorylation in *Caenorhabditis elegans*. *Nat Commun*. 2021;12:4568. [DOI] [PubMed] [PMC]
45. Webb AE, Brunet A. FOXO transcription factors: key regulators of cellular quality control. *Trends Biochem Sci*. 2014;39:159–69. [DOI] [PubMed] [PMC]

46. Zheng L, He S, Wang H, Li J, Liu Y, Liu S. Targeting Cellular Senescence in Aging and Age-Related Diseases: Challenges, Considerations, and the Emerging Role of Senolytic and Senomorphic Therapies. *Aging Dis.* 2024;15:2554–94. [DOI] [PubMed] [PMC]
47. Kroemer G, Maier AB, Cuervo AM, Gladyshev VN, Ferrucci L, Gorbunova V, et al. From geroscience to precision geromedicine: Understanding and managing aging. *Cell.* 2025;188:2043–62. [DOI] [PubMed] [PMC]
48. Pereira B, Correia FP, Alves IA, Costa M, Gameiro M, Martins AP, et al. Epigenetic reprogramming as a key to reverse ageing and increase longevity. *Ageing Res Rev.* 2024;95:102204. [DOI] [PubMed]
49. Papadopoli D, Boulay K, Kazak L, Pollak M, Mallette FA, Topisirovic I, et al. mTOR as a central regulator of lifespan and aging. *F1000Res.* 2019;8:998. [DOI] [PubMed] [PMC]
50. Miwa S, Kashyap S, Chini E, von Zglinicki T. Mitochondrial dysfunction in cell senescence and aging. *J Clin Invest.* 2022;132:e158447. [DOI] [PubMed] [PMC]
51. Tchkonja T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest.* 2013;123:966–72. [DOI] [PubMed] [PMC]
52. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol.* 2010;5:99–118. [DOI] [PubMed] [PMC]
53. Olascoaga S, Konigsberg M, Espinal-Enríquez J, Tovar H, Matadamas-Martínez F, Pérez-Villanueva J, et al. Transcriptomic signatures and network-based methods uncover new senescent cell anti-apoptotic pathways and senolytics. *FEBS J.* 2025;292:1950–71. [DOI] [PubMed] [PMC]
54. Chen S, Gan D, Lin S, Zhong Y, Chen M, Zou X, et al. Metformin in aging and aging-related diseases: clinical applications and relevant mechanisms. *Theranostics.* 2022;12:2722–40. [DOI] [PubMed] [PMC]
55. Oh J, Lee YD, Wagers AJ. Stem cell aging: mechanisms, regulators and therapeutic opportunities. *Nat Med.* 2014;20:870–80. [DOI] [PubMed] [PMC]
56. Tenchov R, Sasso JM, Wang X, Zhou QA. Aging Hallmarks and Progression and Age-Related Diseases: A Landscape View of Research Advancement. *ACS Chem Neurosci.* 2024;15:1–30. [DOI] [PubMed] [PMC]
57. Campbell JM, Bellman SM, Stephenson MD, Lisy K. Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis. *Ageing Res Rev.* 2017;40:31–44. [DOI] [PubMed]
58. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest.* 2001;108:1167–74. [DOI] [PubMed] [PMC]
59. Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest.* 2006;116:1776–83. [DOI] [PubMed] [PMC]
60. Foretz M, Even PC, Viollet B. AMPK Activation Reduces Hepatic Lipid Content by Increasing Fat Oxidation In Vivo. *Int J Mol Sci.* 2018;19:2826. [DOI] [PubMed] [PMC]
61. Srivastava RA, Pinkosky SL, Filippov S, Hanselman JC, Cramer CT, Newton RS. AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. *J Lipid Res.* 2012;53:2490–514. [DOI] [PubMed] [PMC]
62. Zilov AV, Abdelaziz SI, AlShammary A, Al Zahrani A, Amir A, Assaad Khalil SH, et al. Mechanisms of action of metformin with special reference to cardiovascular protection. *Diabetes Metab Res Rev.* 2019;35:e3173. [DOI] [PubMed] [PMC]
63. Mohammed I, Hollenberg MD, Ding H, Triggle CR. A Critical Review of the Evidence That Metformin Is a Putative Anti-Aging Drug That Enhances Healthspan and Extends Lifespan. *Front Endocrinol (Lausanne).* 2021;12:718942. [DOI] [PubMed] [PMC]
64. Kulkarni AS, Gubbi S, Barzilai N. Benefits of Metformin in Attenuating the Hallmarks of Aging. *Cell Metab.* 2020;32:15–30. [DOI] [PubMed] [PMC]

65. Liu XD, Li YG, Wang GY, Bi YG, Zhao Y, Yan ML, et al. Metformin protects high glucose-cultured cardiomyocytes from oxidative stress by promoting NDUFA13 expression and mitochondrial biogenesis via the AMPK signaling pathway. *Mol Med Rep.* 2020;22:5262–70. [DOI] [PubMed] [PMC]
66. Zhong T, Men Y, Lu L, Geng T, Zhou J, Mitsushashi A, et al. Metformin alters DNA methylation genome-wide via the H19/SAHH axis. *Oncogene.* 2017;36:2345–54. [DOI] [PubMed] [PMC]
67. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a Tool to Target Aging. *Cell Metab.* 2016;23:1060–5. [DOI] [PubMed] [PMC]
68. Kukidome D, Nishikawa T, Sonoda K, Imoto K, Fujisawa K, Yano M, et al. Activation of AMP-activated protein kinase reduces hyperglycemia-induced mitochondrial reactive oxygen species production and promotes mitochondrial biogenesis in human umbilical vein endothelial cells. *Diabetes.* 2006;55:120–7. [DOI] [PubMed]
69. Rehman A, Satyam SM, El-Tanani M, Prabhakar S, Kumari R, Shetty P, et al. Metformin Beyond Diabetes: A Precision Gerotherapeutic and Immunometabolic Adjuvant for Aging and Cancer. *Cancers (Basel).* 2025;17:2466. [DOI] [PubMed] [PMC]
70. Zhu Y, Tchkonja T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell.* 2015;14:644–58. [DOI] [PubMed] [PMC]
71. Dai H, Chen R, Gui C, Tao T, Ge Y, Zhao X, et al. Eliminating senescent chondrogenic progenitor cells enhances chondrogenesis under intermittent hydrostatic pressure for the treatment of OA. *Stem Cell Res Ther.* 2020;11:199. [DOI] [PubMed] [PMC]
72. Fan T, Du Y, Zhang M, Zhu AR, Zhang J. Senolytics Cocktail Dasatinib and Quercetin Alleviate Human Umbilical Vein Endothelial Cell Senescence via the TRAF6-MAPK-NF- κ B Axis in a YTHDF2-Dependent Manner. *Gerontology.* 2022;68:920–34. [DOI] [PubMed]
73. Yakubo S, Abe H, Li Y, Kudo M, Kimura A, Wakabayashi T, et al. Dasatinib and Quercetin as Senolytic Drugs Improve Fat Deposition and Exhibit Antifibrotic Effects in the Medaka Metabolic Dysfunction-Associated Steatotic Liver Disease Model. *Diseases.* 2024;12:317. [DOI] [PubMed] [PMC]
74. Rodríguez-Agustín A, Casanova V, Grau-Expósito J, Sánchez-Palomino S, Alcamí J, Climent N. Immunomodulatory Activity of the Tyrosine Kinase Inhibitor Dasatinib to Elicit NK Cytotoxicity against Cancer, HIV Infection and Aging. *Pharmaceutics.* 2023;15:917. [DOI] [PubMed] [PMC]
75. Islam MT, Tuday E, Allen S, Kim J, Trott DW, Holland WL, et al. Senolytic drugs, dasatinib and quercetin, attenuate adipose tissue inflammation, and ameliorate metabolic function in old age. *Aging Cell.* 2023;22:e13767. [DOI] [PubMed] [PMC]
76. Wang Y, Che L, Chen X, He Z, Song D, Yuan Y, et al. Repurpose dasatinib and quercetin: Targeting senescent cells ameliorates postmenopausal osteoporosis and rejuvenates bone regeneration. *Bioact Mater.* 2023;25:13–28. [DOI] [PubMed] [PMC]
77. Nieto M, Konigsberg M, Silva-Palacios A. Quercetin and dasatinib, two powerful senolytics in age-related cardiovascular disease. *Biogerontology.* 2024;25:71–82. [DOI] [PubMed]
78. Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, et al. Senolytics improve physical function and increase lifespan in old age. *Nat Med.* 2018;24:1246–56. [DOI] [PubMed] [PMC]
79. Georgiou N, Kakava MG, Routsis EA, Petsas E, Stavridis N, Freris C, et al. Quercetin: A Potential Polydynamic Drug. *Molecules.* 2023;28:8141. [DOI] [PubMed] [PMC]
80. Targeting Cellular Senescence With Senolytics to Improve Skeletal Health in Older Humans [Internet]. [cited 2025 Sep 11]. Available from: <https://www.clinicaltrials.gov/study/NCT04313634?term=NCT04313634&rank=1>
81. Millar CL, Iloputaife I, Baldyga K, Norling AM, Boulougoura A, Vichos T, et al. A pilot study of senolytics to improve cognition and mobility in older adults at risk for Alzheimer's disease. *EBioMedicine.* 2025;113:105612. [DOI] [PubMed] [PMC]

82. Espinoza SE, Khosla S, Baur JA, de Cabo R, Musi N. Drugs Targeting Mechanisms of Aging to Delay Age-Related Disease and Promote Healthspan: Proceedings of a National Institute on Aging Workshop. *J Gerontol A Biol Sci Med Sci*. 2023;78:53–60. [DOI] [PubMed] [PMC]
83. Justice JN, Nambiar AM, Tchkonja T, LeBrasseur NK, Pascual R, Hashmi SK, et al. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. *EBioMedicine*. 2019;40:554–63. [DOI] [PubMed] [PMC]
84. Alejandra WP, Miriam Irene JP, Fabio Antonio GS, Patricia RR, Elizabeth TA, Aleman-Aguilar JP, et al. Production of monoclonal antibodies for therapeutic purposes: A review. *Int Immunopharmacol*. 2023;120:110376. [DOI] [PubMed]
85. Squarzone S, Schena E, Sabatelli P, Mattioli E, Capanni C, Cenni V, et al. Interleukin-6 neutralization ameliorates symptoms in prematurely aged mice. *Aging Cell*. 2021;20:e13285. [DOI] [PubMed] [PMC]
86. Giuliani A, Prattichizzo F, Micolucci L, Ceriello A, Procopio AD, Rippo MR. Mitochondrial (Dys) Function in Inflammation: Do MitomiRs Influence the Energetic, Oxidative, and Inflammatory Status of Senescent Cells? *Mediators Inflamm*. 2017;2017:2309034. [DOI] [PubMed] [PMC]
87. Rašková M, Lacina L, Kejík Z, Venhauerová A, Skaličková M, Kolář M, et al. The Role of IL-6 in Cancer Cell Invasiveness and Metastasis—Overview and Therapeutic Opportunities. *Cells*. 2022;11:3698. [DOI] [PubMed] [PMC]
88. Soler MF, Abaurrea A, Azcoaga P, Araujo AM, Caffarel MM. New perspectives in cancer immunotherapy: targeting IL-6 cytokine family. *J Immunother Cancer*. 2023;11:e007530. [DOI] [PubMed] [PMC]
89. Tyrrell DJ, Goldstein DR. Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6. *Nat Rev Cardiol*. 2021;18:58–68. [DOI] [PubMed] [PMC]
90. Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol*. 2008;6:e301. [DOI] [PubMed] [PMC]
91. Wang Y, Zhu S, Wei W, Tu Y, Chen C, Song J, et al. Interleukin-6 knockout reverses macrophage differentiation imbalance and alleviates cardiac dysfunction in aging mice. *Aging (Albany NY)*. 2020;12:20184–97. [DOI] [PubMed] [PMC]
92. Tanaka T, Narazaki M, Ogata A, Kishimoto T. A new era for the treatment of inflammatory autoimmune diseases by interleukin-6 blockade strategy. *Semin Immunol*. 2014;26:88–96. [DOI] [PubMed]
93. Nowak KL, Kakkar R, Devalaraja M, Lo L, Park W, Gobburu J, et al. A Phase 1 Randomized Dose-Escalation Study of a Human Monoclonal Antibody to IL-6 in CKD. *Kidney360*. 2021;2:224–35. [DOI] [PubMed] [PMC]
94. Specker C, Aringer M, Burmester GR, Killy B, Hofmann MW, Kellner H, et al. The safety and effectiveness of tocilizumab in elderly patients with rheumatoid arthritis and in patients with comorbidities associated with age. *Clin Exp Rheumatol*. 2022;40:1657–65. [DOI] [PubMed]
95. Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, Richez C, Truchetet ME, Wendling D, et al. Effect of Tocilizumab on Disease Activity in Patients With Active Polymyalgia Rheumatica Receiving Glucocorticoid Therapy: A Randomized Clinical Trial. *JAMA*. 2022;328:1053–62. [DOI] [PubMed] [PMC]
96. Law S, Chaudhuri S. Mesenchymal stem cell and regenerative medicine: regeneration versus immunomodulatory challenges. *Am J Stem Cells*. 2013;2:22–38. [PubMed] [PMC]
97. Yang YK. Aging of mesenchymal stem cells: Implication in regenerative medicine. *Regen Ther*. 2018;9:120–2. [DOI] [PubMed] [PMC]
98. Ermolaeva M, Neri F, Ori A, Rudolph KL. Cellular and epigenetic drivers of stem cell ageing. *Nat Rev Mol Cell Biol*. 2018;19:594–610. [DOI] [PubMed]

99. Steinert AF, Rackwitz L, Gilbert F, Nöth U, Tuan RS. Concise review: the clinical application of mesenchymal stem cells for musculoskeletal regeneration: current status and perspectives. *Stem Cells Transl Med.* 2012;1:237–47. [DOI] [PubMed] [PMC]
100. FDA Approves First Mesenchymal Stromal Cell Therapy to Treat Steroid-refractory Acute Graft-versus-host Disease [Internet]. Cision US Inc.; c2026 [cited 2025 Sep 20]. Available from: <https://www.prnewswire.com/news-releases/fda-approves-first-mesenchymal-stromal-cell-therapy-to-treat-steroid-refractory-acute-graft-versus-host-disease-302335542.html>
101. Kitada M, Dezawa M. Parkinson's disease and mesenchymal stem cells: potential for cell-based therapy. *Parkinsons Dis.* 2012;2012:873706. [DOI] [PubMed] [PMC]
102. Ward MR, Abadeh A, Connelly KA. Concise Review: Rational Use of Mesenchymal Stem Cells in the Treatment of Ischemic Heart Disease. *Stem Cells Transl Med.* 2018;7:543–50. [DOI] [PubMed] [PMC]
103. Hall B, Cho A, Limaye A, Cho K, Khillan J, Kulkarni AB. Genome Editing in Mice Using CRISPR/Cas9 Technology. *Curr Protoc Cell Biol.* 2018;81:e57. [DOI] [PubMed] [PMC]
104. Pelletier S, Gingras S, Green DR. Mouse genome engineering via CRISPR-Cas9 for study of immune function. *Immunity.* 2015;42:18–27. [DOI] [PubMed] [PMC]
105. Qin W, Dion SL, Kutny PM, Zhang Y, Cheng AW, Jillette NL, et al. Efficient CRISPR/Cas9-Mediated Genome Editing in Mice by Zygote Electroporation of Nuclease. *Genetics.* 2015;200:423–30. [DOI] [PubMed] [PMC]
106. Shin HY, Wang C, Lee HK, Yoo KH, Zeng X, Kuhns T, et al. CRISPR/Cas9 targeting events cause complex deletions and insertions at 17 sites in the mouse genome. *Nat Commun.* 2017;8:15464. [DOI] [PubMed] [PMC]
107. Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N, et al. Multiplex genome engineering using CRISPR/Cas systems. *Science.* 2013;339:819–23. [DOI] [PubMed] [PMC]
108. Quadros RM, Miura H, Harms DW, Akatsuka H, Sato T, Aida T, et al. Easi-CRISPR: a robust method for one-step generation of mice carrying conditional and insertion alleles using long ssDNA donors and CRISPR ribonucleoproteins. *Genome Biol.* 2017;18:92. [DOI] [PubMed] [PMC]
109. Davis DJ, McNew JF, Maresca-Fichter H, Chen K, Telugu BP, Bryda EC. Efficient DNA knock-in using AAV-mediated delivery with 2-cell embryo CRISPR-Cas9 electroporation. *Front Genome Ed.* 2023;5:1256451. [DOI] [PubMed] [PMC]
110. Wang W, Zheng Y, Sun S, Li W, Song M, Ji Q, et al. A genome-wide CRISPR-based screen identifies *KAT7* as a driver of cellular senescence. *Sci Transl Med.* 2021;13:eabd2655. [DOI] [PubMed]
111. Huang S, Lau CH, Tin C, Lam RHW. Extended replicative lifespan of primary resting T cells by CRISPR/dCas9-based epigenetic modifiers and transcriptional activators. *Cell Mol Life Sci.* 2024;81:407. [DOI] [PubMed] [PMC]
112. Mostoslavsky R, Chua KF, Lombard DB, Pang WW, Fischer MR, Gellon L, et al. Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell.* 2006;124:315–29. [DOI] [PubMed]
113. Roichman A, Elhanati S, Aon MA, Abramovich I, Di Francesco A, Shahar Y, et al. Restoration of energy homeostasis by SIRT6 extends healthy lifespan. *Nat Commun.* 2021;12:3208. [DOI] [PubMed] [PMC]
114. You W, Zheng W, Weiss S, Chua KF, Steegborn C. Structural basis for the activation and inhibition of Sirtuin 6 by quercetin and its derivatives. *Sci Rep.* 2019;9:19176. [DOI] [PubMed] [PMC]
115. Michishita E, McCord RA, Berber E, Kioi M, Padilla-Nash H, Damian M, et al. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. *Nature.* 2008;452:492–6. [DOI] [PubMed] [PMC]
116. Mao Z, Hine C, Tian X, Van Meter M, Au M, Vaidya A, et al. SIRT6 promotes DNA repair under stress by activating PARP1. *Science.* 2011;332:1443–6. [DOI] [PubMed] [PMC]
117. Toiber D, Erdel F, Bouazoune K, Silberman DM, Zhong L, Mulligan P, et al. SIRT6 recruits SNF2H to DNA break sites, preventing genomic instability through chromatin remodeling. *Mol Cell.* 2013;51:454–68. [DOI] [PubMed] [PMC]

118. Wang X, Li X, Zhou J, Lei Z, Yang X. Fisetin suppresses chondrocyte senescence and attenuates osteoarthritis progression by targeting sirtuin 6. *Chem Biol Interact.* 2024;390:110890. [DOI] [PubMed]
119. Zhong L, D'Urso A, Toiber D, Sebastian C, Henry RE, Vadysirisack DD, et al. The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1 α . *Cell.* 2010;140:280–93. [DOI] [PubMed] [PMC]
120. Tao R, Xiong X, DePinho RA, Deng CX, Dong XC. FoxO3 transcription factor and Sirt6 deacetylase regulate low density lipoprotein (LDL)-cholesterol homeostasis via control of the proprotein convertase subtilisin/kexin type 9 (*Pcsk9*) gene expression. *J Biol Chem.* 2013;288:29252–9. [DOI] [PubMed] [PMC]
121. Wang X, Chen X, Zhang X, Su C, Yang M, He W, et al. A small-molecule inhibitor of PCSK9 transcription ameliorates atherosclerosis through the modulation of FoxO1/3 and HNF1 α . *EBioMedicine.* 2020;52:102650. [DOI] [PubMed] [PMC]
122. Ramteke P, Watson B, Toci M, Tran VA, Johnston S, Tsingas M, et al. Sirt6 deficiency promotes senescence and age-associated intervertebral disc degeneration in mice. *Bone Res.* 2025;13:50. [DOI] [PubMed] [PMC]
123. Liu X, Ren S, Li Z, Hao D, Zhao X, Zhang Z, et al. Sirt6 mediates antioxidative functions by increasing Nrf2 abundance. *Exp Cell Res.* 2023;422:113409. [DOI] [PubMed]
124. Guo Z, Li P, Ge J, Li H. SIRT6 in Aging, Metabolism, Inflammation and Cardiovascular Diseases. *Aging Dis.* 2022;13:1787–822. [DOI] [PubMed] [PMC]
125. McHugh D, Sun B, Gutierrez-Muñoz C, Hernández-González F, Mellone M, Guiho R, et al. COPI vesicle formation and N-myristoylation are targetable vulnerabilities of senescent cells. *Nat Cell Biol.* 2023;25:1804–20. [DOI] [PubMed] [PMC]
126. Aman Y. Targeting COPing liabilities of senescent cells. *Nat Aging.* 2024;4:5. [DOI] [PubMed]
127. Ko A, Han SY, Song J. Dynamics of ARF regulation that control senescence and cancer. *BMB Rep.* 2016;49:598–606. [DOI] [PubMed] [PMC]
128. Lueg GA, Zhang J, Faronato M, Gorelik A, Kallemeijn WW, Falciani F, et al. MYC deregulation sensitizes cancer cells to N-myristoyltransferase inhibition. *Cell Rep.* 2025;44:116180. [DOI] [PubMed]
129. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature.* 1998;391:806–11. [DOI] [PubMed]
130. Bernstein E, Caudy AA, Hammond SM, Hannon GJ. Role for a bidentate ribonuclease in the initiation step of RNA interference. *Nature.* 2001;409:363–6. [DOI] [PubMed]
131. Hammond SM, Bernstein E, Beach D, Hannon GJ. An RNA-directed nuclease mediates post-transcriptional gene silencing in *Drosophila* cells. *Nature.* 2000;404:293–6. [DOI] [PubMed]
132. Buj R, Leon KE, Anguelov MA, Aird KM. Suppression of p16 alleviates the senescence-associated secretory phenotype. *Aging (Albany NY).* 2021;13:3290–312. [DOI] [PubMed] [PMC]
133. Takaya K, Asou T, Kishi K. Downregulation of senescence-associated secretory phenotype by knockdown of secreted frizzled-related protein 4 contributes to the prevention of skin aging. *Aging (Albany NY).* 2022;14:8167–78. [DOI] [PubMed] [PMC]
134. Bleau AM, Jimenez AI, Gramis V, Ruz V, Segerros RA, Vargas B. Clinical trial for SYL1801, a new siRNA-Based Treatment for Neovascular AMD. *Invest Ophthalmol Vis Sci.* 2025;66:697.
135. Hong SW, Park JH, inventors; Olix Pharmaceuticals Inc, assignee. RNAi AGENT TARGETING MYD88 AND USE THEREOF. United States patent US20240093188A1. 2024 Mar 21.
136. Grogan M, Sheikh FH, Sperry BW, Sweetser MT, Capocelli K, Roblin S, et al. Realizing the therapeutic potential of rapid knockdown of transthyretin via RNA interference in transthyretin amyloidosis. *Mol Ther Nucleic Acids.* 2025;36:102590. [DOI] [PubMed] [PMC]
137. Lathe R, Sapronova A, Kotelevtsev Y. Atherosclerosis and Alzheimer-diseases with a common cause? Inflammation, oxysterols, vasculature. *BMC Geriatr.* 2014;14:36. [DOI] [PubMed] [PMC]

138. Adams D, Wixner J, Polydefkis M, Berk JL, Conceição IM, Dispenzieri A, et al.; patisiran Global OLE study group. Five-Year Results With Patisiran for Hereditary Transthyretin Amyloidosis With Polyneuropathy: A Randomized Clinical Trial With Open-Label Extension. *JAMA Neurol.* 2025;82:228–36. [DOI] [PubMed] [PMC]
139. Wang Y, Zhou J, Yang Q, Li X, Qiu Y, Zhang Y, et al. Therapeutic siRNA targeting PLIN2 ameliorates steatosis, inflammation, and fibrosis in steatotic liver disease models. *J Lipid Res.* 2024;65:100635. [DOI] [PubMed] [PMC]
140. Justice JN, Ferrucci L, Newman AB, Aroda VR, Bahnson JL, Divers J, et al. A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. *Geroscience.* 2018;40:419–36. [DOI] [PubMed] [PMC]
141. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet.* 2018;19:371–84. [DOI] [PubMed]
142. Belsky DW, Caspi A, Arseneault L, Baccarelli A, Corcoran DL, Gao X, et al. Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm. *Elife.* 2020;9:e54870. [DOI] [PubMed] [PMC]
143. Wagner KH, Cameron-Smith D, Wessner B, Franzke B. Biomarkers of Aging: From Function to Molecular Biology. *Nutrients.* 2016;8:338. [DOI] [PubMed] [PMC]
144. Ho AD, Wagner W, Mahlknecht U. Stem cells and ageing. The potential of stem cells to overcome age-related deteriorations of the body in regenerative medicine. *EMBO Rep.* 2005;6:S35–8. [DOI] [PubMed] [PMC]
145. Hodrosky N, Cacho G, Ahmed F, Mudireddy R, Wen Y, Nembhard K, et al. The Pharmaceutical Price Regulation Crisis: Implications on Antidepressant Access for Low-Income Americans. arXiv:2506.14849 [Preprint]. 2025 [cited 2025 Sep 25]. Available from: <https://doi.org/10.48550/arXiv.2506.14849>
146. Gallini J, Baucom Z, Tripodis Y. Cognitive factor-based selection increases power in Alzheimer’s dementia randomized clinical trials. arXiv:2503.16044 [Preprint]. 2025 [cited 2025 Oct 1]. Available from: <https://doi.org/10.48550/arXiv.2503.16044>
147. Cabañero-Garcia E, Martinez-Lacoba R, Pardo-Garcia I, Amo-Saus E. Barriers to health, social and long-term care access among older adults: a systematic review of reviews. *Int J Equity Health.* 2025;24:72. [DOI] [PubMed] [PMC]
148. How Might Longevity Therapies Affect Social and Economic Inequality? [Internet]. Sustainability Directory; c2024 [cited 2025 Oct 1]. Available from: <https://lifestyle.sustainability-directory.com/question/how-might-longevity-therapies-affect-social-and-economic-inequality/>