

Assessing mechanisms and evidence of a causal role for cellular senescence and somatic mutations in aging

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Keywords: cellular senescence, somatic mutations, aging, DNA damage, SASP

Received: February 27, 2026

Accepted: July 27, 2026

Published: August 26, 2026

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ABSTRACT

Understanding the primary molecular and cellular drivers of aging and how they trigger systemic functional decline remains a fundamental challenge. This review focuses on two proposed drivers of aging, cellular senescence and somatic DNA mutations, critically discusses the evidence for their association with organismal aging, and appraises their causal contribution to it. Several studies support the notion that cellular senescence can cause aging, acting through cell-intrinsic and, likely more significantly, cell-extrinsic mechanisms such as the senescence-associated secretory phenotype. Differently, the mutational burden is strongly correlated with aging, but we argue that the causal contribution of altered DNA sequences to age-related functional decline remains difficult to untangle from its originating genotoxic events.

INTRODUCTION

Aging is a complex biological process driven by numerous underlying mechanisms. This brief review aims to summarize and critically appraise the evidence implicating an association or a causal role for cellular senescence and somatic DNA mutations in organismal aging, using necessity and sufficiency as key criteria for causal inference. Moreover, this article discusses the plausible molecular mechanisms through which these processes can translate into systemic functional effects, making an impact on tissue dysfunction, healthspan, and lifespan.

Senescent cells as drivers of aging

Although necessarily reductive, one of the most impactful discoveries of Dr. Judith Campisi's influential research was the serendipitous identification of senescent cells as positive for the enzymatic activity widely known as senescence-associated β -galacto-

sidase [1]. This finding enabled the visualization and quantification of senescent cells, leading to the observation of an association between their abundance and the individual's age, later confirmed in several human tissues [2]. However, the low frequency at which senescent cells are often detected in aged tissues [3], together with the substantial variability in estimates across tissues and markers [4], was initially difficult to reconcile with a substantial effect on systemic aging. The full impact of senescent cells on organismal functional decline of aging became apparent when Campisi made a second breakthrough discovery by describing the senescence-associated secretory phenotype (SASP) [5, 6]. The identification of SASP extended the relevance of cellular senescence from being a cell-intrinsic feature, which primarily impairs proliferation, to a cell-extrinsic one in which senescent cells actively communicate with the surrounding tissue, strengthening the mechanistic plausibility of cellular senescence as a driver of aging. Subsequently, Campisi's group [7] and others [8]

provided compelling evidence that cellular senescence is required for wound healing and multiple aging phenotypes by developing genetically engineered mouse models in which senescent cells can be eliminated. Senescent cell clearance in mice resulted in delayed onset or attenuation of age-related pathologies, including sarcopenia, cataracts, and lipodystrophy, and improved overall healthspan [8–11], with a study also reporting an increase in median and maximal lifespan [9]. The use of these mouse models paved the way for the later testing of pharmacological treatments to kill senescent cells (a process termed senolysis) [12–14], confirming and extending the initial conclusions and laying the groundwork for therapeutic developments and a rapidly expanding biotechnology industry [15]. The observation that an intraperitoneal injection of less than one million senescent cells (thus less than 1 cell out of $\sim 10^6$ in a mouse body) impairs physical function [14] or that an intradermal transplant of senescent cells induces frailty and cognitive decline [16] in young mice supports the idea that even a low senescent cell burden is able to compromise healthspan, acting systemically. This does not eliminate important caveats: senescent cells are heterogeneous and no universal marker exists, thus a unified definition of senescent cells remains under discussion [4] and their removal is generally limited to specific senescent cells subsets, dependent on the approach exploited. Nevertheless, also thanks to Campisi's work, cellular senescence is now widely considered a causal contributor to aging [17], an inference supported by evidence spanning association, necessity, and sufficiency in animal models.

The organism-level impact of senescent cells is exerted through multiple mechanisms. One is by imposing a stable proliferative arrest in cells, which therefore cannot replace dying or otherwise eliminated cells, ultimately compromising tissue homeostasis and regenerative capacity. This cell-autonomous effect of cellular senescence is particularly impactful when it ensues in stem cells. Indeed, senescent somatic stem cells display decreased regenerative function [17, 18] and altered differentiation [19, 20], impacting tissues because of their hierarchical role. Accordingly, a recent study demonstrated that mesenchymal progenitor cells engineered to be resistant to cellular senescence can rejuvenate multiple organs in primates [21]. Beyond its role in stem cells, cell-intrinsic cellular senescence can also affect the organism's functions at large when occurring in differentiated cells that play critical systemic roles. This is the case, for instance, of cells regulating systemic metabolism [22], circulation [23], or immune function [24]. Notably, when immune cells become senescent [24], their capacity to clear other

senescent cells is compromised, generating a feedback mechanism that exacerbates the accumulation of senescent cells, inducing age-related dysfunction in several tissues and decreasing median lifespan in mice [25].

However, the major process by which senescent cells can cause systemic aging phenotypes is through the already mentioned SASP, a complex secretory program by which senescent cells signal and remodel their microenvironment. The SASP has the ability to reinforce autocrine (where the cell signals to itself) and fuel paracrine (where the cell signals to neighboring cells) cellular senescence in a contagious manner – indeed, normal cells can undergo senescence [26, 27] when exposed to SASP, generating a self-amplifying mechanism. The SASP exerts its cell-extrinsic role of altering the microenvironment via immune and tissue remodeling mechanisms. With respect to the immune-mediated perturbation of the cellular context, the secretion of pro-inflammatory cytokines and chemokines of SASP generates a chronic state of low-grade inflammation (termed inflammaging in the context of aging [28]) and immunosuppression, which can both be associated with aging and related diseases, including cancer [18, 29]. Regarding the SASP's contribution to aging by disrupting the tissue organization, it can induce cell death [30] or influence the differentiation of nearby cells [31]. Moreover, the SASP can remodel the extracellular matrix through the release of proteases and matrix metalloproteinases [18, 29], and can lead to the disruption of intercellular barriers via degradation of junctional proteins [32]. Finally, SASP can profoundly alter the tissue microenvironment to the point of inducing fibrosis, characterized by increased tissue stiffness and loss of elasticity [33].

Altogether, this body of evidence supports the conclusion that cells undergoing cellular senescence significantly contribute to organismal aging, reducing healthspan and median lifespan in the experimental settings studied. However, these findings largely derive from animal models, and sustained clinical benefit from senolysis remains unproven in large, well-controlled trials in humans. Although the relative contribution of cell-intrinsic limited proliferative capacity may play a limited role at the single-cell level, this process likely exerts systemic effects when it disrupts stem cell hierarchies or organism-scale functions, such as immunity, indicating that cell-autonomous defects can impact systemically even beyond paracrine signaling. However, the most significant contribution of cellular senescence to aging likely derives from systemic mechanisms triggered by the paracrine SASP, such as inflammation and tissue remodeling.

Somatic mutations as drivers of aging

A few years before the discovery of cellular senescence by Hayflick and Moorhead in 1961 [34], a part of the scientific community postulated a causal role of the accumulation of somatic DNA mutations in aging [35, 36]. Recent advances in genomic sequencing technologies, especially those enabling the detection of somatic mutations with extremely low variant allele frequency (VAF) [37], have reinvigorated this hypothesis [38, 39], buttressing it with novel data that support an association between mutation accumulation and aging. Indeed, the burden of mutations, including single-nucleotide variants (SNVs) and small insertions and deletions (indels), increases in various normal tissues with age [40–46] at a constant rate [47]. Mitochondrial SNVs also become more abundant with age [48]. A modest age-related accumulation of structural variants (SVs) was shown in normal intestinal crypts [40, 46], but these events remain technically more difficult to assess comprehensively in normal somatic tissues. Moreover, some mutational signatures – specific patterns of mutations that reflect distinct underlying biological processes – display a clock-like behavior, accumulating linearly with age [49]. Interestingly, the species' maximal lifespan is inversely correlated with the mutation accumulation rate [50], suggesting the existence of a maximal mutation threshold in the lifetime beyond which tissue homeostasis is compromised to the point of system failure and death. Since mutations are the result of DNA damage or inaccurate DNA replication, it is not surprising that DNA repair ability correlates with species' maximal longevity [51, 52]. The DREAM repressive complex was recently identified as a potential determinant of this relationship, as lower DREAM activity associates with reduced somatic mutation burden and longer lifespan [53]. In addition, DNA repair efficiency decreases with age [54, 55], and patients with genetic syndromes defective in DNA repair often display accelerated aging signs [55, 56], although this is not always the case. For instance, mutations that diminish DNA polymerase ϵ and δ proofreading ability [57] or MutY DNA glycosylase capacity of removing mismatched bases in the DNA [58] confer a higher mutational burden but no signs of premature aging in patients, demonstrating that the presence of mutated cells is not sufficient to cause age-related phenotypes. The observation that a hypermutated mitochondrial DNA due to proofreading-deficient versions of mitochondrial DNA polymerase was associated with accelerated aging in the past may be explained by a respiratory chain dysfunction [59, 60]. However, it cannot be excluded that the mutational burden required to elicit overt premature-aging phenotypes in tissues is substantially higher than that

sufficient to promote tumorigenesis; thus, in some contexts, cancer development may precede and therefore mask the manifestation of other age-related phenotypes. Furthermore, direct tests of necessity via selective elimination of mutated cells, without concomitantly interfering with DNA damage signaling and cellular senescence pathways, remain scarce.

The mechanisms by which low-abundant somatic mutations, in the form of an altered DNA sequence, may contribute to aging are likely cell-intrinsic, by perturbing gene expression and genome functions. Indeed, it has been proposed that mutations induce a so-called transcriptional noise through the alteration of the gene regulatory network, thereby impairing cell functionality [61, 62]. Additionally, as for cellular senescence, the mutation burden may have a systemic impact when associated with stem cells, for instance mutated satellite cells in the muscle display lower proliferative and differentiative potential [63], or with immune cells, such as mutated natural killer cells that have decreased cytotoxic ability [64]. Finally, certain somatic mutations confer proliferative advantage, resulting in the clonal expansion of the cell population bearing the driver mutation, generating a mosaic of clones in otherwise apparently normal tissues. This genome mosaicism may contribute to aging by novel mechanisms, generating heterogeneity and compromising tissue homeostasis [65]. Indeed, recent studies reported that in several aged but seemingly healthy tissues [66], including skin [67, 68], esophagus [69, 70], and blood [71], a considerable proportion of cells derive from multiple clones that expanded due to mutation in cancer-related genes.

Notwithstanding the large body of evidence that shows an association between mutation accumulation and aging, direct causal evidence proving that somatic mutations are necessary and sufficient for functional decline is difficult to establish. This is because DNA damage events preceding mutations also lead to DNA damage signaling, a process that is a well-recognized trigger of cellular senescence [72] and aging [38, 55, 73, 74]. Thus, DNA damage induces both its signaling and its repair, but only if the latter is incorrect, it will cause a mutation (Figure 1). The observed correlation between mutation burden and age is thus hard to separate from senescence-inducing DNA damage signaling events. Therefore, DNA damage, DNA damage signaling, and DNA mutations represent distinct yet co-occurring biological events, and disentangling the individual contribution to aging of each of them is difficult. In other words, a plausible hypothesis is that the drivers of aging may be the signaling events that arise upon DNA damage generation, with mutations being another accidental outcome. Therefore, a fundamental question is the following: when DNA damage ensues, is it the related signaling that

promotes aging or the mutations that may result from inaccurate repair? The observations made in DNA repair-deficient animal models and genetic human syndromes do not allow to distinguish between these two, not necessarily mutually exclusive, possibilities. Noteworthy, inactivation of p53, a downstream DNA damage signaling nodal gene, attenuates the phenotypes of some accelerated aging syndromes, including those derived from telomere dysfunction [75] and DNA repair deficiency [76]. Similarly, inhibition of the DNA damage response at telomeres has been shown to ameliorate age-related hematopoietic and pulmonary dysfunction [77, 78], without lengthening critically short telomeres, which represent the source of DNA damage signaling. These observations argue in favor of DNA damage signaling as the driver of aging phenotypes in these contexts, since p53 loss or signaling inhibition is unlikely to reduce mutation burden in these settings – although the pleiotropic roles of p53 must be borne in mind.

Accumulating DNA damage with age can cause progressive tissue dysfunction as it affects the two main DNA functions: replication and transcription, both of which depend on an intact template. DNA lesions interfere with the DNA duplication process in

proliferating cells, causing replication stress and DNA damage signaling, potentially triggering cellular senescence and stem cell exhaustion [79]. DNA damage also physically hampers transcription elongation in a variety of species, ranging from nematodes to humans, and tissues, including in post-mitotic cells [80]. As DNA damage is proportional to gene length, it preferentially leads to a genome-wide decline in the expression of long genes in aging. Transcription stress explains over half of all gene expression changes associated with aging in the transcription profiles of many organs, potentially affecting numerous cellular functions, as transcription is essential for all cellular processes [80, 81]. Indeed, the gene length-dependent transcription decline correlates with pro- and anti-aging interventions [82], including dietary restriction [83].

In conclusion, disentangling the relative contribution of somatic mutations and DNA damage signaling to aging remains challenging. Thus, while mutations represent a renowned cause of cancer, their intrinsic impact on organisms' functional decline, although plausible, still needs ultimate proof. The notion that DNA damage, through its signaling, acts as an apical event driving senescence, while being also a powerful source of

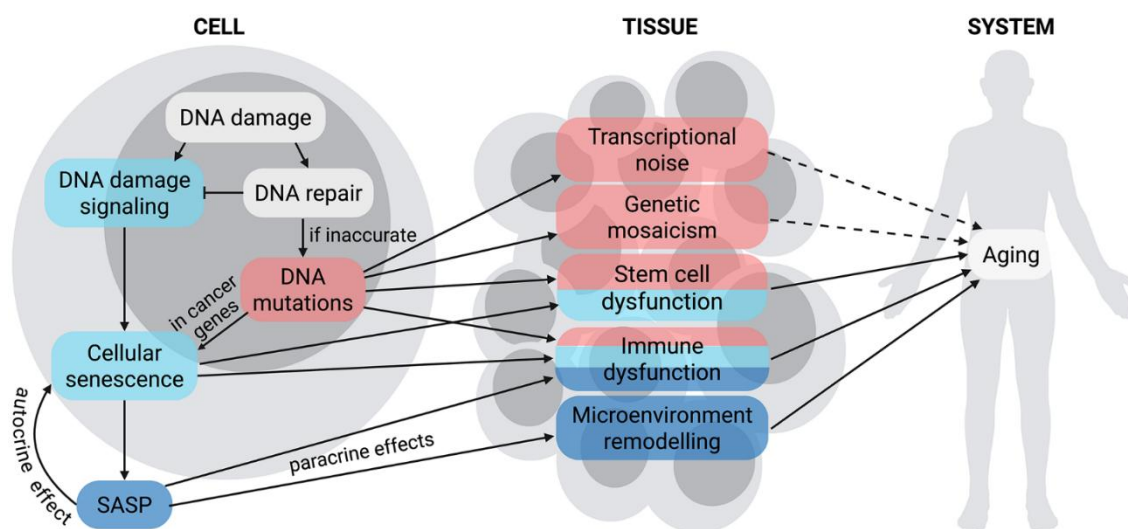


Figure 1. The DNA damage cascade and its effects on aging from the molecular to the systemic level. In the nucleus of the cell, DNA damage triggers protective mechanisms, initiating DNA damage signaling and coordinating DNA repair. The primary outcome of DNA damage signaling can be the induction of cellular senescence, whereas failed or inaccurate DNA repair can lead to DNA mutations. When a mutation occurs in oncogenes or tumor suppressor genes, it can trigger oncogene-induced senescence, representing an intersection between these two events. At the tissue level, mutations may generate consequential effects, including transcriptional noise, genetic mosaicism, and immune and stem cell dysfunction. Cellular senescence too can impact the stem and immune compartments and have a broader effect due to the senescence-associated secretory phenotype (SASP), which propagates in an autocrine and paracrine fashion, inducing tissue remodeling and potentially exacerbating immune dysfunction. At the systemic level, an aberrant microenvironment, immune response, and regenerative capacity can contribute to age-related functional decline, and it has been speculated the same potential for transcriptional noise and clone formation. In the figure, cellular senescence with its associated mechanisms of aging is depicted in light blue, SASP in blue, and somatic mutations in red; solid arrows indicate links that are more strongly supported by experimental evidence, while dotted arrows represent more speculative links.

mutations, places it at the nexus between these two much-studied aging-associated events.

Open questions and concluding remarks

Cellular senescence is widely recognized as a driver of age-related phenotypes, intrinsically linked to other aging hallmarks such as telomere dysfunction, chronic inflammation, and stem cell exhaustion [84]. Differently, the potential interplay of somatic mutations (as distinct from the broader concept of genome instability) with the other hallmarks of aging is still unprobed, and the contribution of an altered DNA sequence to aging needs deeper understanding. More broadly, our discussion of cellular senescence and somatic mutations illustrates the wider challenge of biogerontology in distinguishing driver from passenger mechanisms of aging [85].

Cellular senescence and mutation accumulation are distinct events, and it is presently unclear how these pathways relate to each other. Notably, among the limited evidence connecting the two paradigms, an important discovery is that they can functionally converge when mutations cause oncogene activation and consequent cellular senescence [86–90]. In addition, although senescent cells are mitotically arrested and thus immune to replication errors, they may still accumulate mutations due to increased production of genotoxic reactive oxygen species and the reactivation of retrotransposons, which can cause insertional mutagenesis [56]. The observation that senescent cells repress several DNA repair genes and have decreased repair efficiency upon irradiation [91], combined with their resistance to apoptosis, provide the bases for mutation accumulation in these cells. In line with this evidence, cells that underwent replicative senescence have been reported to bear more SNVs and small indels, and to be more frequently aneuploid compared to early-passage cells, although a contribution of the additional DNA replication rounds required to reach replicative senescence could not be excluded [92].

Distinguishing persistent DNA damage signaling from mutational burden remains a challenge to determine the specific contribution of mutations to the aging process. A decisive experiment would be to induce changes in the DNA sequence with minimal DNA damage to test whether the mutational load is sufficient to produce age-related phenotypes. One experimental option would be to reduce replication fidelity, for instance via impaired polymerase proofreading or mismatch repair, which in patients is generally not associated with accelerated aging signs [57, 58]; another option would be to use base editors in the form of adenosine deaminases fused to catalytically impaired Cas9 to introduce widespread

substitutions without DNA cleavage [93] – however, some degree of DNA damage signaling cannot be excluded even in these settings. A conceptually related approach has been achieved in animals that are born with a very high inherited mutational load, as shown indirectly in a study where serially recloned mice carrying a high mutational burden were reported to appear healthy and to have normal lifespans, although the authors did not assess DNA damage levels [94]. Regarding the potential impact of genome mosaicism, lineage-tracing combined with omics techniques would help find a correlation of mutational load and clone size with tissue dysfunction.

Defining the interplay between cellular senescence and mutations remains a significant challenge, with a limited number of dedicated studies in the literature, because both processes derive from DNA damage and are difficult to disentangle. Such analyses are further complicated by the low abundance of senescent cells in aged tissues and by the impossibility of expanding these arrested cells. Therefore, elucidating this relationship represents a largely unexplored area of research in the field, one that will refine our understanding of the aging network.

AUTHOR CONTRIBUTIONS

Both authors conceived, structured, wrote, and edited the manuscript.

ACKNOWLEDGMENTS

We apologize to the authors of any relevant studies that we may not have cited for space reasons.

Grammarly.com, DeepSeek.com, and Microsoft 365 Copilot were used in a supervised manner for literature search and language editing. The figure was created with BioRender.com.

CONFLICTS OF INTEREST

F. d'A. d.F. is a founder and investor in TAG Therapeutics, a company dedicated to treating telomere pathologies and age-related disorders. L. A. T. declares no competing interests.

FUNDING

L. A. T. was supported by AIRC (28211). F. d' A. d.F.'s laboratory is supported by: ERC advanced grant (TELORNAGING - 835103); ERC POC (TELOVACCINE - 101113229); AIRC-IG (30471); Telethon (GMR23T2007); Next Generation EU, in the context of the National Recovery and Resilience Plan,

REFERENCES

- Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O. A biomarker that identifies senescent human cells in culture and in aging skin *in vivo*. *Proc Natl Acad Sci USA*. 1995; 92:9363–7. <https://doi.org/10.1073/pnas.92.20.9363> PMID: [7568133](https://pubmed.ncbi.nlm.nih.gov/7568133/)
- Tuttle CS, Waaijer ME, Slee-Valentijn MS, Stijnen T, Westendorp R, Maier AB. Cellular senescence and chronological age in various human tissues: A systematic review and meta-analysis. *Aging Cell*. 2020; 19:e13083. <https://doi.org/10.1111/acer.13083> PMID: [31808308](https://pubmed.ncbi.nlm.nih.gov/31808308/)
- Ogrodnik M. Cellular aging beyond cellular senescence: Markers of senescence prior to cell cycle arrest *in vitro* and *in vivo*. *Aging Cell*. 2021; 20:e13338. <https://doi.org/10.1111/acer.13338> PMID: [33711211](https://pubmed.ncbi.nlm.nih.gov/33711211/)
- Ogrodnik M, Carlos Acosta J, Adams PD, d'Adda di Fagagna F, Baker DJ, Bishop CL, Chandra T, Collado M, Gil J, Gorgoulis V, Gruber F, Hara E, Jansen-Dürr P, et al. Guidelines for minimal information on cellular senescence experimentation *in vivo*. *Cell*. 2024; 187:4150–75. <https://doi.org/10.1016/j.cell.2024.05.059> PMID: [39121846](https://pubmed.ncbi.nlm.nih.gov/39121846/)
- Krtolica A, Parrinello S, Lockett S, Desprez PY, Campisi J. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. *Proc Natl Acad Sci USA*. 2001; 98:12072–7. <https://doi.org/10.1073/pnas.211053698> PMID: [11593017](https://pubmed.ncbi.nlm.nih.gov/11593017/)
- Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol*. 2008; 6:2853–68. <https://doi.org/10.1371/journal.pbio.0060301> PMID: [19053174](https://pubmed.ncbi.nlm.nih.gov/19053174/)
- Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, Laberge RM, Vijg J, Van Steeg H, Dollé ME, Hoeijmakers JH, de Bruin A, Hara E, Campisi J. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. *Dev Cell*. 2014; 31:722–33. <https://doi.org/10.1016/j.devcel.2014.11.012> PMID: [25499914](https://pubmed.ncbi.nlm.nih.gov/25499914/)
- Baker DJ, Wijshake T, Tchkonja T, LeBrasseur NK, Childs BG, van de Sluis B, Kirkland JL, van Deursen JM. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature*. 2011; 479:232–6. <https://doi.org/10.1038/nature10600> PMID: [22048312](https://pubmed.ncbi.nlm.nih.gov/22048312/)
- Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, Saltness RA, Jeganathan KB, Verzosa GC, Pezeshki A, Khazaie K, Miller JD, van Deursen JM. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. *Nature*. 2016; 530:184–9. <https://doi.org/10.1038/nature16932> PMID: [26840489](https://pubmed.ncbi.nlm.nih.gov/26840489/)
- Jeon OH, Kim C, Laberge RM, Demaria M, Rathod S, Vasserot AP, Chung JW, Kim DH, Poon Y, David N, Baker DJ, van Deursen JM, Campisi J, Elisseeff JH. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. *Nat Med*. 2017; 23:775–81. <https://doi.org/10.1038/nm.4324> PMID: [28436958](https://pubmed.ncbi.nlm.nih.gov/28436958/)
- Kaur G, Muthumalage T, Rahman I. Clearance of senescent cells reverts the cigarette smoke-induced lung senescence and airspace enlargement in p16-3MR mice. *Aging Cell*. 2023; 22:e13850. <https://doi.org/10.1111/acer.13850> PMID: [37078230](https://pubmed.ncbi.nlm.nih.gov/37078230/)
- Zhu Y, Tchkonja T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, Palmer AK, Ikeno Y, Hubbard GB, Lenburg M, O'Hara SP, LaRusso NF, Miller JD, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*. 2015; 14:644–58. <https://doi.org/10.1111/acer.12344> PMID: [25754370](https://pubmed.ncbi.nlm.nih.gov/25754370/)
- Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, Janakiraman K, Sharpless NE, Ding S, Feng W, Luo Y, Wang X, Aykin-Burns N, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. *Nat Med*. 2016; 22:78–83. <https://doi.org/10.1038/nm.4010> PMID: [26657143](https://pubmed.ncbi.nlm.nih.gov/26657143/)
- Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, Inman CL, Ogrodnik MB, Hachfeld CM, Fraser DG, Onken JL, Johnson KO, Verzosa GC, et al. Senolytics improve physical function and increase lifespan in old age. *Nat Med*. 2018; 24:1246–56. <https://doi.org/10.1038/s41591-018-0092-9> PMID: [29988130](https://pubmed.ncbi.nlm.nih.gov/29988130/)
- Chaib S, Tchkonja T, Kirkland JL. Cellular senescence and senolytics: the path to the clinic. *Nat Med*. 2022; 28:1556–68. <https://doi.org/10.1038/s41591-022-01923-y> PMID: [35953721](https://pubmed.ncbi.nlm.nih.gov/35953721/)
- Franco AC, Martini H, Victorelli S, Lagnado AB, Wyles SP, Rowsey JL, Pirius N, Woo SH, Costa DG, Chaib S, Tullius SG, Tchkonja T, Kirkland JL, et al. Senescent cell transplantation into the skin induces age-related

- peripheral dysfunction and cognitive decline. *Aging Cell*. 2025; 24:e14340.
<https://doi.org/10.1111/ace1.14340> PMID:39374134
17. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021; 22:75–95.
<https://doi.org/10.1038/s41580-020-00314-w> PMID:33328614
 18. Birch J, Gil J. Senescence and the SASP: many therapeutic avenues. *Genes Dev*. 2020; 34:1565–76.
<https://doi.org/10.1101/gad.343129.120> PMID:33262144
 19. Mohri Y, Nie J, Morinaga H, Kato T, Aoto T, Yamanashi T, Nanba D, Matsumura H, Kirino S, Kobiyama K, Ishii KJ, Hayashi M, Suzuki T, et al. Antagonistic stem cell fates under stress govern decisions between hair greying and melanoma. *Nat Cell Biol*. 2025; 27:1647–59.
<https://doi.org/10.1038/s41556-025-01769-9> PMID:41053225
 20. Schneider L, Pellegatta S, Favaro R, Pisati F, Roncaglia P, Testa G, Nicolis SK, Finocchiaro G, d'Adda di Fagagna F. DNA damage in mammalian neural stem cells leads to astrocytic differentiation mediated by BMP2 signaling through JAK-STAT. *Stem Cell Reports*. 2013; 1:123–38.
<https://doi.org/10.1016/j.stemcr.2013.06.004> PMID:24052948
 21. Lei J, Xin Z, Liu N, Ning T, Jing Y, Qiao Y, He Z, Jiang M, Yang Y, Zhang Z, Zhao L, Li J, Lv D, et al. Senescence-resistant human mesenchymal progenitor cells counter aging in primates. *Cell*. 2025; 188:5039–61.e35.
<https://doi.org/10.1016/j.cell.2025.05.021> PMID:40516525
 22. Zhang H, Zhou H, Shen X, Lin X, Zhang Y, Sun Y, Zhou Y, Zhang L, Zhang D. The role of cellular senescence in metabolic diseases and the potential for senotherapeutic interventions. *Front Cell Dev Biol*. 2023; 11:1276707.
<https://doi.org/10.3389/fcell.2023.1276707> PMID:37868908
 23. Bloom SI, Islam MT, Lesniewski LA, Donato AJ. Mechanisms and consequences of endothelial cell senescence. *Nat Rev Cardiol*. 2023; 20:38–51.
<https://doi.org/10.1038/s41569-022-00739-0> PMID:35853997
 24. Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, Cheng Q, Luo P, Zhang Y, Han X. Immunosenescence: molecular mechanisms and diseases. *Signal Transduct Target Ther*. 2023; 8:200.
<https://doi.org/10.1038/s41392-023-01451-2> PMID:37179335
 25. Yousefzadeh MJ, Flores RR, Zhu Y, Schmiechen ZC, Brooks RW, Trussoni CE, Cui Y, Angelini L, Lee KA, McGowan SJ, Burrack AL, Wang D, Dong Q, et al. An aged immune system drives senescence and ageing of solid organs. *Nature*. 2021; 594:100–05.
<https://doi.org/10.1038/s41586-021-03547-7> PMID:33981041
 26. Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, Athineos D, Kang TW, Lasitschka F, Andrulis M, Pascual G, Morris KJ, Khan S, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. *Nat Cell Biol*. 2013; 15:978–90.
<https://doi.org/10.1038/ncb2784> PMID:23770676
 27. Vitorcelli S, Lagnado A, Halim J, Moore W, Talbot D, Barrett K, Chapman J, Birch J, Ogrodnik M, Meves A, Pawlikowski JS, Jurk D, Adams PD, et al. Senescent human melanocytes drive skin ageing via paracrine telomere dysfunction. *EMBO J*. 2019; 38:e101982.
<https://doi.org/10.15252/embj.2019101982> PMID:31633821
 28. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014; 69:S4–9.
<https://doi.org/10.1093/gerona/glu057> PMID:24833586
 29. Wang B, Han J, Elisseeff JH, Demaria M. The senescence-associated secretory phenotype and its physiological and pathological implications. *Nat Rev Mol Cell Biol*. 2024; 25:958–78.
<https://doi.org/10.1038/s41580-024-00727-x> PMID:38654098
 30. Hom LM, Sun S, Campbell J, Liu P, Culbert S, Murphy IM, Schafer ZT. A role for fibroblast-derived SASP factors in the activation of pyroptotic cell death in mammary epithelial cells. *J Biol Chem*. 2023; 299:104922.
<https://doi.org/10.1016/j.jbc.2023.104922> PMID:37321449
 31. Wiley CD, Velarde MC, Lecot P, Liu S, Sarnoski EA, Freund A, Shirakawa K, Lim HW, Davis SS, Ramanathan A, Gerencser AA, Verdin E, Campisi J. Mitochondrial Dysfunction Induces Senescence with a Distinct Secretory Phenotype. *Cell Metab*. 2016; 23:303–14.
<https://doi.org/10.1016/j.cmet.2015.11.011> PMID:26686024
 32. Chen Y, Zhou Y, Bai Y, Jia K, Zhang H, Chen Q, Song M, Dai Y, Shi J, Chen Z, Yan X, Shen Y. Macrophage-derived CTSS drives the age-dependent disruption of the blood-CSF barrier. *Neuron*. 2025; 113:1082–97.e8.
<https://doi.org/10.1016/j.neuron.2025.01.023> PMID:40015275

33. O'Reilly S, Tsou PS, Varga J. Senescence and tissue fibrosis: opportunities for therapeutic targeting. *Trends Mol Med*. 2024; 30:1113–25.
<https://doi.org/10.1016/j.molmed.2024.05.012>
PMID:38890028
34. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res*. 1961; 25:585–621.
[https://doi.org/10.1016/0014-4827\(61\)90192-6](https://doi.org/10.1016/0014-4827(61)90192-6)
PMID:13905658
35. Szilard L. ON THE NATURE OF THE AGING PROCESS. *Proc Natl Acad Sci USA*. 1959; 45:30–45.
<https://doi.org/10.1073/pnas.45.1.30> PMID:16590351
36. Failla G. The aging process and cancerogenesis. *Ann N Y Acad Sci*. 1958; 71:1124–40.
<https://doi.org/10.1111/j.1749-6632.1958.tb46828.x>
PMID:13583876
37. Ren P, Zhang J, Vijg J. Somatic mutations in aging and disease. *Geroscience*. 2024; 46:5171–89.
<https://doi.org/10.1007/s11357-024-01113-3>
PMID:38488948
38. Vijg J. From DNA damage to mutations: All roads lead to aging. *Ageing Res Rev*. 2021; 68:101316.
<https://doi.org/10.1016/j.arr.2021.101316>
PMID:33711511
39. Chatsirisupachai K, de Magalhães JP. Somatic mutations in human ageing: New insights from DNA sequencing and inherited mutations. *Ageing Res Rev*. 2024; 96:102268.
<https://doi.org/10.1016/j.arr.2024.102268>
PMID:38490496
40. Lee-Six H, Olafsson S, Ellis P, Osborne RJ, Sanders MA, Moore L, Georgakopoulos N, Torrente F, Noorani A, Goddard M, Robinson P, Coorens TH, O'Neill L, et al. The landscape of somatic mutation in normal colorectal epithelial cells. *Nature*. 2019; 574:532–7.
<https://doi.org/10.1038/s41586-019-1672-7>
PMID:31645730
41. Lawson AR, Abascal F, Nicola PA, Lensing SV, Roberts AL, Kalantzis G, Baez-Ortega A, Brzozowska N, El-Sayed Moustafa JS, Vaitkute D, Jakupovic B, Nessa A, Wadge S, et al. Somatic mutation and selection at population scale. *Nature*. 2025; 647:411–20.
<https://doi.org/10.1038/s41586-025-09584-w>
PMID:41062696
42. Zhang L, Dong X, Lee M, Maslov AY, Wang T, Vijg J. Single-cell whole-genome sequencing reveals the functional landscape of somatic mutations in B lymphocytes across the human lifespan. *Proc Natl Acad Sci USA*. 2019; 116:9014–9.
<https://doi.org/10.1073/pnas.1902510116>
PMID:30992375
43. Huang Z, Sun S, Lee M, Maslov AY, Shi M, Waldman S, Marsh A, Siddiqui T, Dong X, Peter Y, Sadoughi A, Shah C, Ye K, et al. Single-cell analysis of somatic mutations in human bronchial epithelial cells in relation to aging and smoking. *Nat Genet*. 2022; 54:492–8.
<https://doi.org/10.1038/s41588-022-01035-w>
PMID:35410377
44. Brazhnik K, Sun S, Alani O, Kinkhabwala M, Wolkoff AW, Maslov AY, Dong X, Vijg J. Single-cell analysis reveals different age-related somatic mutation profiles between stem and differentiated cells in human liver. *Sci Adv*. 2020; 6:eaax2659.
<https://doi.org/10.1126/sciadv.aax2659>
PMID:32064334
45. Ganz J, Luquette LJ, Bizzotto S, Miller MB, Zhou Z, Bohrsen CL, Jin H, Tran AV, Viswanadham VV, McDonough G, Brown K, Chahine Y, Chhouk B, et al. Contrasting somatic mutation patterns in aging human neurons and oligodendrocytes. *Cell*. 2024; 187:1955–70.e23.
<https://doi.org/10.1016/j.cell.2024.02.025>
PMID:38503282
46. Forsberg LA, Rasi C, Razzaghian HR, Pakalapati G, Waite L, Thilbeault KS, Ronowicz A, Wineinger NE, Tiwari HK, Boomsma D, Westerman MP, Harris JR, Lyle R, et al. Age-related somatic structural changes in the nuclear genome of human blood cells. *Am J Hum Genet*. 2012; 90:217–28.
<https://doi.org/10.1016/j.ajhg.2011.12.009>
PMID:22305530
47. Abascal F, Harvey LM, Mitchell E, Lawson AR, Lensing SV, Ellis P, Russell AJ, Alcantara RE, Baez-Ortega A, Wang Y, Kwa EJ, Lee-Six H, Cagan A, et al. Somatic mutation landscapes at single-molecule resolution. *Nature*. 2021; 593:405–10.
<https://doi.org/10.1038/s41586-021-03477-4>
PMID:33911282
48. Gupta R, Durham TJ, Chau G, Kanai M, Uddin MM, Lu W, Argentieri MA, Karczewski KJ, Howrigan D, Natarajan P, Zhou W, Neale BM, Mootha VK. Mechanism of age-related accumulation of mtDNA mutations in human blood. *Nature*. 2026. [Epub ahead of print].
<https://doi.org/10.1038/s41586-026-10569-6>
PMID:42203880
49. Alexandrov LB, Jones PH, Wedge DC, Sale JE, Campbell PJ, Nik-Zainal S, Stratton MR. Clock-like mutational processes in human somatic cells. *Nat Genet*. 2015; 47:1402–7.
<https://doi.org/10.1038/ng.3441> PMID:26551669
50. Cagan A, Baez-Ortega A, Brzozowska N, Abascal F, Coorens TH, Sanders MA, Lawson AR, Harvey LM, Bhosle S, Jones D, Alcantara RE, Butler TM, Hooks Y,

- et al. Somatic mutation rates scale with lifespan across mammals. *Nature*. 2022; 604:517–24.
<https://doi.org/10.1038/s41586-022-04618-z>
PMID:35418684
51. Zhang L, Dong X, Tian X, Lee M, Abulaeva J, Firсанov D, Lee SG, Maslov AY, Gladyshev VN, Seluanov A, Gorbunova V, Vijg J. Maintenance of genome sequence integrity in long- and short-lived rodent species. *Sci Adv*. 2021; 7:eabj3284.
<https://doi.org/10.1126/sciadv.abj3284>
PMID:34705500
 52. Tian X, Firсанov D, Zhang Z, Cheng Y, Luo L, Tomblin G, Tan R, Simon M, Henderson S, Steffan J, Goldfarb A, Tam J, Zheng K, et al. SIRT6 Is Responsible for More Efficient DNA Double-Strand Break Repair in Long-Lived Species. *Cell*. 2019; 177:622–38.e22.
<https://doi.org/10.1016/j.cell.2019.03.043>
PMID:31002797
 53. Koch Z, Nandi SP, Licon K, Bujarrabal-Dueso A, Meyer DH, Saeed S, Perampalam P, Dick FA, Schumacher B, Alexandrov LB, Ideker T. DREAM repressive activity links somatic mutation, lifespan and disease. *Nat Aging*. 2026; 6:1267–80.
<https://doi.org/10.1038/s43587-026-01132-z>
PMID:42230995
 54. Gorbunova V, Seluanov A, Mao Z, Hine C. Changes in DNA repair during aging. *Nucleic Acids Res*. 2007; 35:7466–74.
<https://doi.org/10.1093/nar/gkm756>
PMID:17913742
 55. Niedernhofer LJ, Gurkar AU, Wang Y, Vijg J, Hoeijmakers JH, Robbins PD. Nuclear Genomic Instability and Aging. *Annu Rev Biochem*. 2018; 87:295–322.
<https://doi.org/10.1146/annurev-biochem-062917-012239> PMID:29925262
 56. Zhao Y, Simon M, Seluanov A, Gorbunova V. DNA damage and repair in age-related inflammation. *Nat Rev Immunol*. 2023; 23:75–89.
<https://doi.org/10.1038/s41577-022-00751-y>
PMID:35831609
 57. Robinson PS, Coorens TH, Palles C, Mitchell E, Abascal F, Olafsson S, Lee BC, Lawson AR, Lee-Six H, Moore L, Sanders MA, Hewinson J, Martin L, et al. Increased somatic mutation burdens in normal human cells due to defective DNA polymerases. *Nat Genet*. 2021; 53:1434–42.
<https://doi.org/10.1038/s41588-021-00930-y>
PMID:34594041
 58. Robinson PS, Thomas LE, Abascal F, Jung H, Harvey LM, West HD, Olafsson S, Lee BC, Coorens TH, Lee-Six H, Butlin L, Lander N, Truscott R, et al. Inherited MUTYH mutations cause elevated somatic mutation rates and distinctive mutational signatures in normal human cells. *Nat Commun*. 2022; 13:3949.
<https://doi.org/10.1038/s41467-022-31341-0>
PMID:35803914
 59. Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, Bohlooly-Y M, Gidlöf S, Oldfors A, Wibom R, Törnelli J, Jacobs HT, Larsson NG. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature*. 2004; 429:417–23.
<https://doi.org/10.1038/nature02517> PMID:15164064
 60. Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, Hofer T, Seo AY, Sullivan R, Jobling WA, Morrow JD, Van Remmen H, Sedivy JM, et al. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science*. 2005; 309:481–4.
<https://doi.org/10.1126/science.1112125>
PMID:16020738
 61. Bahar R, Hartmann CH, Rodriguez KA, Denny AD, Busuttill RA, Dollé ME, Calder RB, Chisholm GB, Pollock BH, Klein CA, Vijg J. Increased cell-to-cell variation in gene expression in ageing mouse heart. *Nature*. 2006; 441:1011–4.
<https://doi.org/10.1038/nature04844> PMID:16791200
 62. Shlien A, Raine K, Fuligni F, Arnold R, Nik-Zainal S, Dronov S, Mamanova L, Rosic A, Ju YS, Cooke SL, Ramakrishna M, Papaemmanuil E, Davies HR, et al., and ICGC Breast Cancer Working Group, Oslo Breast Cancer Research Consortium. Direct Transcriptional Consequences of Somatic Mutation in Breast Cancer. *Cell Rep*. 2016; 16:2032–46.
<https://doi.org/10.1016/j.celrep.2016.07.028>
PMID:27498871
 63. Franco I, Johansson A, Olsson K, Vrtačnik P, Lundin P, Helgadóttir HT, Larsson M, Revêchon G, Bosia C, Pagnani A, Provero P, Gustafsson T, Fischer H, Eriksson M. Somatic mutagenesis in satellite cells associates with human skeletal muscle aging. *Nat Commun*. 2018; 9:800.
<https://doi.org/10.1038/s41467-018-03244-6>
PMID:29476074
 64. Rodriguez-Sevilla JJ, Ganan-Gomez I, Kumar B, Thongon N, Ma F, Chien KS, Kim YJ, Yang H, Loghavi S, Tan R, Adema V, Li Z, Tanaka T, et al. Natural killer cells' functional impairment drives the immune escape of pre-malignant clones in early-stage myelodysplastic syndromes. *Nat Commun*. 2025; 16:3450.
<https://doi.org/10.1038/s41467-025-58662-0>
PMID:40216768
 65. Vijg J, Dong X. Pathogenic Mechanisms of Somatic Mutation and Genome Mosaicism in Aging. *Cell*. 2020; 182:12–23.

- <https://doi.org/10.1016/j.cell.2020.06.024>
PMID:32649873
66. Evans EJ Jr, DeGregori J. Cells with Cancer-associated Mutations Overtake Our Tissues as We Age. *Aging Cancer*. 2021; 2:82–97.
<https://doi.org/10.1002/aac2.12037>
PMID:34888527
 67. Martincorena I, Roshan A, Gerstung M, Ellis P, Van Loo P, McLaren S, Wedge DC, Fullam A, Alexandrov LB, Tubio JM, Stebbings L, Menzies A, Widaa S, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. *Science*. 2015; 348:880–6.
<https://doi.org/10.1126/science.aaa6806>
PMID:25999502
 68. Jonason AS, Kunala S, Price GJ, Restifo RJ, Spinelli HM, Persing JA, Leffell DJ, Tarone RE, Brash DE. Frequent clones of p53-mutated keratinocytes in normal human skin. *Proc Natl Acad Sci USA*. 1996; 93:14025–9.
<https://doi.org/10.1073/pnas.93.24.14025>
PMID:8943054
 69. Martincorena I, Fowler JC, Wabik A, Lawson AR, Abascal F, Hall MW, Cagan A, Murai K, Mahbubani K, Stratton MR, Fitzgerald RC, Handford PA, Campbell PJ, et al. Somatic mutant clones colonize the human esophagus with age. *Science*. 2018; 362:911–7.
<https://doi.org/10.1126/science.aau3879>
PMID:30337457
 70. Yokoyama A, Kakiuchi N, Yoshizato T, Nannya Y, Suzuki H, Takeuchi Y, Shiozawa Y, Sato Y, Aoki K, Kim SK, Fujii Y, Yoshida K, Kataoka K, et al. Age-related remodelling of oesophageal epithelia by mutated cancer drivers. *Nature*. 2019; 565:312–7.
<https://doi.org/10.1038/s41586-018-0811-x>
PMID:30602793
 71. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, Lindsley RC, Mermel CH, Burt N, Chavez A, Higgins JM, Moltchanov V, Kuo FC, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014; 371:2488–98.
<https://doi.org/10.1056/NEJMoa1408617>
PMID:25426837
 72. d'Adda di Fagagna F. Living on a break: cellular senescence as a DNA-damage response. *Nat Rev Cancer*. 2008; 8:512–22.
<https://doi.org/10.1038/nrc2440>
PMID:18574463
 73. Schumacher B, Pothof J, Vijg J, Hoeijmakers JH. The central role of DNA damage in the ageing process. *Nature*. 2021; 592:695–703.
<https://doi.org/10.1038/s41586-021-03307-7>
PMID:33911272
 74. Panier S, Wang S, Schumacher B. Genome Instability and DNA Repair in Somatic and Reproductive Aging. *Annu Rev Pathol*. 2024; 19:261–90.
<https://doi.org/10.1146/annurev-pathmechdis-051122-093128> PMID:37832947
 75. Chin L, Artandi SE, Shen Q, Tam A, Lee SL, Gottlieb GJ, Greider CW, DePinho RA. p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis. *Cell*. 1999; 97:527–38.
[https://doi.org/10.1016/s0092-8674\(00\)80762-x](https://doi.org/10.1016/s0092-8674(00)80762-x)
PMID:10338216
 76. Ceccaldi R, Parmar K, Mouly E, Delord M, Kim JM, Regairaz M, Pla M, Vasquez N, Zhang QS, Pondarre C, Peffault de Latour R, Gluckman E, Cavazzana-Calvo M, et al. Bone marrow failure in Fanconi anemia is triggered by an exacerbated p53/p21 DNA damage response that impairs hematopoietic stem and progenitor cells. *Cell Stem Cell*. 2012; 11:36–49.
<https://doi.org/10.1016/j.stem.2012.05.013>
PMID:22683204
 77. Oppezzo A, Sepe S, Cicio G, Cancila V, Sasso E, Conti A, Marinelli E, Cabrini M, Pallavi R, Iacomino N, Simoni M, Malyshev D, Boggio S, et al. Therapeutic inhibition of telomeric DNA damage response rescues hematopoietic dysfunction driven by telomere shortening and aging. *Nat Aging*. 2026; 6:1377–94.
<https://doi.org/10.1038/s43587-026-01136-9>
 78. Rossiello F, Cicio G, Sepe S, Mancheno-Ferris A, Cancila V, Castellini A, Rey F, Bertolazzi G, Oppezzo A, Marinelli E, Cabrini M, di Lillo A, Tavella S, et al. The telomeric DNA damage response as a therapeutic target in idiopathic pulmonary fibrosis. *EMBO Mol Med*. 2026.
<https://doi.org/10.1038/s44321-026-00500-x>
 79. Herr LM, Schaffer ED, Fuchs KF, Datta A, Brosh RM Jr. Replication stress as a driver of cellular senescence and aging. *Commun Biol*. 2024; 7:616.
<https://doi.org/10.1038/s42003-024-06263-w>
PMID:38777831
 80. Gyenis A, Chang J, Demmers JJ, Bruens ST, Barnhoorn S, Brandt RM, Baar MP, Raseta M, Derks KW, Hoeijmakers JH, Pothof J. Genome-wide RNA polymerase stalling shapes the transcriptome during aging. *Nat Genet*. 2023; 55:268–79.
<https://doi.org/10.1038/s41588-022-01279-6>
PMID:36658433
 81. Stoeger T, Grant RA, McQuattie-Pimentel AC, Anekalla KR, Liu SS, Tejedor-Navarro H, Singer BD, Abdala-Valencia H, Schwake M, Tetreault MP, Perlman H, Balch WE, Chandel NS, et al. Aging is associated with a systemic length-associated transcriptome imbalance. *Nat Aging*. 2022; 2:1191–206.

<https://doi.org/10.1038/s43587-022-00317-6>
PMID:37118543

82. Ibañez-Solé O, Barrio I, Izeta A. Age or lifestyle-induced accumulation of genotoxicity is associated with a length-dependent decrease in gene expression. *iScience*. 2023; 26:106368.
<https://doi.org/10.1016/j.isci.2023.106368>
PMID:37013186
83. Vermeij WP, Dollé ME, Reiling E, Jaarsma D, Payan-Gomez C, Bombardieri CR, Wu H, Roks AJ, Botter SM, van der Eerden BC, Youssef SA, Kuiper RV, Nagarajah B, et al. Restricted diet delays accelerated ageing and genomic stress in DNA-repair-deficient mice. *Nature*. 2016; 537:427–31.
<https://doi.org/10.1038/nature19329> PMID:27556946
84. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell*. 2023; 186:243–78.
<https://doi.org/10.1016/j.cell.2022.11.001>
PMID:36599349
85. de Magalhães JP. Distinguishing between driver and passenger mechanisms of aging. *Nat Genet*. 2024; 56:204–11.
<https://doi.org/10.1038/s41588-023-01627-0>
PMID:38242993
86. Di Micco R, Fumagalli M, Cicalese A, Piccinin S, Gasparini P, Luise C, Schurra C, Garre' M, Nuciforo PG, Bensimon A, Maestro R, Pelicci PG, d'Adda di Fagagna F. Oncogene-induced senescence is a DNA damage response triggered by DNA hyper-replication. *Nature*. 2006; 444:638–42.
<https://doi.org/10.1038/nature05327> PMID:17136094
87. Michaloglou C, Vredeveld LC, Soengas MS, Denoyelle C, Kuilman T, van der Horst CM, Majoor DM, Shay JW, Mooi WJ, Peeper DS. BRAF^{V600E}-associated senescence-like cell cycle arrest of human naevi. *Nature*. 2005; 436:720–4.
<https://doi.org/10.1038/nature03890> PMID:16079850
88. Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. *Cell*. 1997; 88:593–602.
89. Braig M, Lee S, Loddenkemper C, Rudolph C, Peters AH, Schlegelberger B, Stein H, Dörken B, Jenuwein T, Schmitt CA. Oncogene-induced senescence as an initial barrier in lymphoma development. *Nature*. 2005; 436:660–5.
<https://doi.org/10.1038/nature03841>
PMID:16079837
90. Chen Z, Trotman LC, Shaffer D, Lin HK, Dotan ZA, Niki M, Koutcher JA, Scher HI, Ludwig T, Gerald W, Cordon-Cardo C, Pandolfi PP. Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. *Nature*. 2005; 436:725–30.
<https://doi.org/10.1038/nature03918>
PMID:16079851
91. Frey Y, Haj M, Ziv Y, Elkon R, Shiloh Y. Broad repression of DNA repair genes in senescent cells identified by integration of transcriptomic data. *Nucleic Acids Res*. 2025; 53:gkae1257.
<https://doi.org/10.1093/nar/gkae1257>
PMID:39739833
92. Zhang L, De Cecco M, Lee M, Hao X, Maslov AY, Montagna C, Campisi J, Dong X, Sedivy JM, Vijg J. Analysis of Somatic Mutations in Senescent Cells Using Single-Cell Whole-Genome Sequencing. *Aging Biol*. 2023; 1:20230005.
<https://doi.org/10.59368/agingbio.20230005>
PMID:39421602
93. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*. 2016; 533:420–4.
<https://doi.org/10.1038/nature17946>
PMID:27096365
94. Wakayama S, Ito D, Inoue R, Ooga M, Toshishige M, Satoh Y, Shiura H, Kohda T, Uchimura A, Wakayama T. Limitations of serial cloning in mammals. *Nat Commun*. 2026; 17:2495.
<https://doi.org/10.1038/s41467-026-69765-7>
PMID:41876466