Cellular Aging: Mechanisms and Interventions

Howard Ze

Abstract

Aging is a complex process that happens in our bodies, especially inside our cells, increasing vulnerability to diseases and death. The importance of studying aging lies in its direct association with major age-related diseases such as Alzheimer's, cardiovascular disorders, and cancer. Given the rapid growth of the aging population worldwide, understanding these mechanisms is crucial for developing strategies to promote healthier longevity and reduce the socioeconomic burden of age-related diseases. Recent advances in biotechnology and geroscience have identified promising interventions to delay aging and extend lifespan. Emerging therapies, including stem cell treatments and gene-editing technologies and pharmacological interventions such as drugs that inhibit the activity of protein kinases that promote cell senescence. This review examines cellular aging and highlights current strategies, drawn from molecular biology, genetics, and clinical research, that aim to delay aging and promote sustained health and longevity.

Introduction

Aging is a complex biological process characterized by the progressive decline of physiological functions, leading to increased vulnerability to diseases and death (Titorenko, 2018a). It affects multiple cellular and molecular pathways, including DNA damage, mitochondrial dysfunction, and cellular senescence, which collectively contribute to tissue and organ deterioration (Sarkar & Fisher, 2006a). DNA damage is a constant threat because nucleic acids are chemically unstable under physiological conditions and vulnerable to attack by endogenous and environmental factors. To combat this, all organisms possess highly conserved mechanisms to detect and repair DNA damage (Yousefzadeh et al., 2021). Mitochondrial dysfunction, operationally defined as a decreased respiratory capacity per mitochondrion together with a decreased mitochondrial membrane potential, typically accompanied by increased production of oxygen free radicals, is a cause and a consequence of cellular senescence and figures prominently in multiple feedback loops that induce and maintain the senescent phenotype (Miwa et al., 2022b). Finally, cellular senescence is an irreversible cycle arrest which can be triggered by a variety of factors (Jeyapalan & Sedivy, 2008).

The importance of studying aging lies in its direct association with major age-related diseases such as Alzheimer's, cardiovascular disorders, and cancer (DiLoreto & Murphy, 2015). Research has shown that aging is not merely a passive accumulation of damage but an active process regulated by genetic and epigenetic factors (Ferrucci et al., 2020). According to the World Health Organization (WHO), by 2030, one in six people worldwide will be aged 60 years or older.(Titorenko, 2018a) Furthermore, the population aged 60 years and older is expected to increase from 1 billion in 2020 to 1.4 billion in 2030. In addition, by 2050, this population is expected to double (2.1 billion).(Titorenko, 2018a) Similarly, the number of people aged 80 years and older is expected to triple between 2020 and 2050 and reach 426 million (Noto,

2023). As the global population ages, understanding the mechanisms behind aging becomes crucial for developing interventions to improve healthspan (Ferrucci et al., 2020).

This review will systematically examine the molecular mechanisms driving cellular aging (Titorenko, 2018c) and their clinical manifestations(the observable and measurable signs and symptoms that indicate the presence of a disease or medical condition) in major age-related diseases (DiLoreto & Murphy, 2015) while also evaluating emerging therapeutic strategies to extend the human healthspan (Ferrucci et al., 2020). We will first describe fundamental hallmarks of aging - including telomere attrition (Richter & Zglinicki, 2007a), mitochondrial dysfunction (Miwa et al., 2022a), and DNA damage accumulation (Yousefzadeh et al., 2021) - before discussing their pathological consequences and current intervention approaches.

Biological signs of aging

Telomere shortening

Telomere shortening represents one of the fundamental molecular mechanisms underlying cellular aging. Telomeres are protective nucleotide sequences at the ends of chromosomes that progressively erode with each cell division due to the end-replication problem, where DNA polymerase cannot fully copy the lagging strand (DiLoreto & Murphy, 2015). When telomeres reach a critically short length, they lose their protective capping function, triggering either cellular senescence - a permanent state of growth arrest - or programmed cell death (apoptosis) (Ferrucci et al., 2020). This process contributes significantly to age-related tissue dysfunction and organ decline.

Several factors can accelerate the rate of telomere shortening beyond normal replicative aging. Oxidative stress plays a particularly damaging role because telomeres are especially vulnerable to reactive oxygen species due to their limited DNA repair capabilities (Richter & Zglinicki, 2007a). Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the cellular antioxidant defense capacity, leading to damage of biomolecules and disruption of redox homeostasis."(Sies et al., 2017) Chronic inflammation further exacerbates telomere attrition through the sustained production of inflammatory cytokines that increase oxidative damage to telomeric DNA (Ferrucci et al., 2020). Notably, tissues with high proliferative demands, such as the immune system, skin, and intestinal lining, experience particularly rapid telomere shortening, leading to their functional decline with advancing age (Trifunovic & Larsson, 2008a).

The consequences of telomere shortening manifest differently between humans and mouse models. In humans, shortened telomeres strongly correlate with various age-related pathologies (Ferrucci et al., 2020). Immunosenescence, characterized by diminished immune function, develops as immune cells lose their replicative capacity (Ferrucci et al., 2020). However, most laboratory mice maintain long telomeres throughout life and express telomerase in somatic cells, making them less susceptible to replicative senescence (Yamada-Fukunaga et al., 2013). Telomerase is an enzyme that elongates telomeres by adding repetitive DNA sequences to chromosome ends, thereby preserving replicative capacity and delaying cellular senescence (Ferrucci et al., n.d.). In humans, telomerase activity is typically restricted to germline and stem

cells, and its absence in most somatic cells contributes to age-related telomere shortening, which is strongly associated with immunosenescence and other pathologies (Ferrucci et al., 2020). In contrast, laboratory mice exhibit fundamental differences in telomere biology: they possess inherently longer telomeres and maintain widespread telomerase expression in somatic tissues throughout life, making them less prone to replicative senescence under normal conditions (Ferrucci et al., 2020). To study human-relevant telomere dysfunction, researchers rely on genetically modified mouse models, such as telomerase-deficient strains or late-generation mice with critically shortened telomeres, which better recapitulate age-related decline (Ferrucci et al., 2020). These interspecies differences highlight the need for caution when translating telomere-targeted therapies, as interventions like telomerase activation may have divergent effects—potentially mitigating aging in humans but carrying elevated oncogenic risks compared to mice (Ferrucci et al., 2020). Current research explores potential interventions targeting telomere maintenance, including telomerase activation therapies and antioxidant strategies, though these approaches must balance potential benefits against cancer risks (Richter & Zglinicki, 2007b).

Mitochondrial Dysfunction

Mitochondrial dysfunction during aging primarily stems from accumulated damage to mitochondrial DNA (mtDNA). Unlike nuclear DNA, mtDNA lacks protective histones and has limited repair capacity, making it particularly susceptible to mutations caused by reactive oxygen species (ROS) generated during oxidative phosphorylation (Yousefzadeh et al., 2021). These mutations impair the electron transport chain's function, reducing ATP production efficiency while paradoxically increasing ROS leakage - creating a vicious cycle of oxidative damage (DiLoreto & Murphy, 2015).

The quality control mechanisms for mitochondria also deteriorate with age. Normally, damaged mitochondria are removed through mitophagy, a selective form of autophagy. (Trifunovic & Larsson, 2008a)However, this process becomes less efficient in aging cells, allowing dysfunctional mitochondria to accumulate (Trifunovic & Larsson, 2008b). Additionally, the dynamic processes of mitochondrial fusion and fission, which are crucial for maintaining a healthy mitochondrial network, become dysregulated. This leads to either excessive fragmentation or abnormal elongation of mitochondria, both of which compromise cellular energy production (McGuire, 2019).

The cumulative effect of these changes is a progressive decline in mitochondrial membrane potential, reduced oxidative phosphorylation capacity, and increased oxidative stress. This mitochondrial dysfunction not only affects energy production but also disrupts calcium buffering and apoptotic signaling, contributing to cellular senescence and tissue degeneration (Boveris & Navarro, 2008).

The insights gained from these comparative studies in mice are crucial for elucidating the pathophysiological pathways shared with humans.(Breuer et al., 2012). Inactivation of the Ndufs4 gene directly affects the encoding of mitochondrial complex I, resulting in a phenotype that includes many of the symptoms seen in humans suffering the same affliction: low birth

weight, followed by subsequent failure to thrive, partial to total blindness, and impairments in motor function.(Breuer et al., 2012). The Harlequin mouse model, resulting from a mutation in the gene encoding Apoptosis Inducing Factor, exhibits characteristics similar to the Ndufs4 mouse, including severe cerebellar ataxia, optic tract dysfunctions, and an increased risk of hypertrophic cardiomyopathy, which are clinical features also observed in human patients with mitochondrial disorders.

DNA Damage Accumulation

DNA damage accumulation is a hallmark of aging that occurs through multiple mechanisms. The primary sources of DNA damage include endogenous reactive oxygen species (ROS) produced during normal cellular metabolism, which cause oxidative lesions such as 8-oxoguanine and thymine glycol (Gensler & Bernstein, 1981a). These oxidative lesions are particularly problematic because they can lead to mutations if not properly repaired before DNA replication occurs (Gensler & Bernstein, 1981a).

The aging process is associated with a decline in the efficiency of DNA repair systems. Base excision repair (BER), which handles small base lesions, a DNA lesion is a structural or chemical alteration to DNA that can disrupt normal cellular processes, and nucleotide excision repair (NER), which deals with bulky lesions, both become less effective with age (Schumacher et al., 2021). This reduced repair capacity allows DNA damage to accumulate over time, contributing to genomic instability (Schumacher et al., 2021).

The accumulation of DNA damage with age has significant consequences for tissue function. In post-mitotic cells like neurons, unrepaired DNA damage can lead to transcriptional silencing and functional decline (Gensler & Bernstein, 1981b). In proliferating tissues, it can lead to either replicative senescence or potentially malignant transformation (Gensler & Bernstein, 1981a).

Tissue Degeneration

DNA damage accumulation represents a fundamental mechanism driving cellular aging processes. The hematopoietic system and skeletal muscle exhibit exceptional aging sensitivity due to stem cell depletion (Yun, 2015). Hematopoietic stem cells accumulate DNA damage, causing immune dysfunction (Colvin et al., 2017a), while muscle satellite : skeletal muscle stem cells located between the muscle fiber's outer membrane and its surrounding connective tissue. Cell failure leads to sarcopenia (Boveris & Navarro, 2008). These tissues share high metabolic rates and proliferative demands that amplify oxidative stress (Trifunovic & Larsson, 2008b). The post-mitotic brain also shows marked vulnerability, with neurons accumulating lesions and protein aggregates (Castellani et al., 2010a). As cells age, they experience progressive genomic instability due to the gradual buildup of various DNA lesions – DNA lesions represent discrete biochemical alterations to DNA structure that compromise genomic integrity, distinct from large-scale mutational events (Gensler & Bernstein, 1981a). These molecular injuries include oxidized bases like 8-oxoguanine, single-strand breaks, and crosslinks that arise

primarily from endogenous reactive oxygen species during normal metabolism including double-strand breaks, and oxidative base modifications (Fibroblasts, 2021a). This damage primarily originates from endogenous sources, particularly reactive oxygen species (ROS) generated during normal metabolic processes (Trifunovic & Larsson, 2008c).

The cellular response to DNA damage becomes increasingly impaired with age. Key DNA repair pathways, including base excision repair and nucleotide excision repair, show reduced efficiency in aged cells (Yousefzadeh et al., 2021). This decline in repair capacity creates a vicious cycle where unrepaired damage leads to further genomic instability and cellular dysfunction (Fibroblasts, 2021b).

Persistent DNA damage triggers cellular senescence through activation of the p53 pathway, representing an important anti-cancer mechanism that nonetheless contributes to tissue aging (Trifunovic & Larsson, 2008c). The accumulation of senescent cells in tissues leads to chronic inflammation and disrupts normal tissue homeostasis (Yousefzadeh et al., 2021). Certain brain regions and organs show early vulnerability to aging. The hippocampus and prefrontal cortex degenerate first, impairing memory and executive function (Sengoku, 2020). The cardiovascular system declines through arterial stiffening and reduced cardiac output (Camici & Liberale, 2017a), while muscles undergo sarcopenia due to satellite cell depletion (Yun, 2015). These patterns reflect tissue-specific combinations of oxidative stress and replicative demands (Trifunovic & Larsson, 2008c).

How Aging Leads to Diseases

Aging simultaneously undermines neurological and physical health through distinct yet overlapping pathways. Alzheimer's disease exemplifies neural decline, characterized by amyloid plaques and neurofibrillary tangles that disrupt cognition (Knopman et al., 2021a), while cardiovascular disease manifests through atherosclerotic plaques and vascular remodeling (Nabel, 2003). Both conditions share roots in chronic inflammation and protein homeostasis failure (Ferrucci et al., 2020).

Alzheimer's Disease

Alzheimer's disease specifically involves two core aging hallmarks: mitochondrial dysfunction and DNA damage. Neurons accumulate mtDNA mutations that impair energy metabolism (Boveris & Navarro, 2008), while nuclear DNA lesions trigger aberrant cell cycle re-entry in post-mitotic cells (Gensler & Bernstein, 1981a). These processes synergize with amyloid toxicity to accelerate neurodegeneration (Castellani et al., 2010b).

Alzheimer's disease (AD) is characterized by two main pathological features: amyloid-beta plaques and neurofibrillary tangles in the brain (Knopman et al., 2021a). These abnormal protein accumulations lead to progressive neuronal damage and cognitive decline, particularly affecting memory functions. The disease typically begins with memory impairment and gradually affects other cognitive abilities (Sengoku, 2020). As it progresses, patients experience increasing difficulties with daily activities and often develop behavioral changes (Castellani et

al., 2010a).Current treatments focus on managing symptoms through medications like cholinesterase inhibitors, along with addressing related health conditions(Ulep et al., 2018a) .

Clinically, AD typically presents with episodic memory impairment that progresses to involve other cognitive domains (Sengoku, 2020). The disease course spans years to decades, with increasing functional impairment in activities of daily living (Ulep et al., 2018a). Behavioral symptoms such as apathy, agitation, and sleep disturbances commonly emerge as the disease advances(Ulep et al., 2018b). Vascular risk factors including hypertension, diabetes, and hyperlipidemia contribute to AD pathogenesis and may accelerate cognitive decline (Knopman et al., 2021b) The presence of cardiovascular disease has been associated with increased risk of developing AD (Sengoku, 2020). Management focuses on symptomatic treatment with cholinesterase inhibitors and NMDA receptor antagonists, along with addressing comorbid conditions (Ulep et al., 2018a).

Recent advances in single-cell sequencing technologies have revolutionized our understanding of Alzheimer's disease (AD) pathogenesis at cellular resolution. These approaches have revealed unprecedented heterogeneity among neuronal and glial cell populations in AD brains (Wang et al., 2022a). Single-cell RNA sequencing has identified distinct transcriptional signatures in vulnerable neuron subtypes, particularly those in the entorhinal cortex and hippocampus (Olah et al., 2020a).

The technology has uncovered novel microglial subpopulations with disease-specific activation states in AD. A unique microglial phenotype expressing neurodegeneration-associated genes (DAM) appears closely associated with amyloid plaque pathology (Xu & Jia, 2021). These microglia show altered phagocytic capacity and inflammatory responses that may contribute to disease progression (Wang et al., 2022b).

Single-cell analyses have also revealed cell-type specific responses to tau pathology. Tau pathology is characterized by the aggregation of abnormally phosphorylated tau protein into paired helical filaments (PHFs), which form neurofibrillary tangles (NFTs), a hallmark of Alzheimer's disease and related tauopathies (Iqbal et al., 2005). Neurons accumulating pathological tau exhibit distinct metabolic and stress response pathways compared to their healthy counterparts (Olah et al., 2020a). Furthermore, non-neuronal cells including astrocytes and oligodendrocytes show disease-associated transcriptional changes that may exacerbate neuronal dysfunction (Olah et al., 2020a). These findings are transforming our understanding of AD as a complex interplay of multiple cell types in the brain microenvironment (Wang et al., 2022b).

Single-cell sequencing has revolutionized aging research by enabling high-resolution analysis of cellular heterogeneity in the brain and other tissues.(Shapiro et al., 2013) By profiling individual cells, this technology reveals age-related transcriptional changes, epigenetic drift, and somatic mutations that bulk sequencing misses.(Iqbal et al., 2005) In neurodegenerative contexts, it has uncovered distinct subpopulations of neurons and glia with varying vulnerability to oxidative stress and protein aggregation.(Iqbal et al., 2005) Studies leveraging single-cell approaches have linked mitochondrial dysfunction and dysregulated proteostasis—key hallmarks of aging—to specific cell types in aged brains.(Shapiro et al., 2013) These insights refine our

understanding of aging mechanisms and pave the way for targeted interventions against age-related neurological decline (Shapiro et al., 2013).

Cardiovascular Diseases

Cardiovascular diseases (CVD) represent a spectrum of disorders affecting the heart and blood vessels, with atherosclerosis being the most common underlying pathology (Nabel, 2003). The development of atherosclerotic plaques involves chronic inflammation, endothelial dysfunction, and lipid accumulation within arterial walls (Colvin et al., 2017a). These pathological changes progressively narrow blood vessels and may ultimately lead to acute coronary syndromes through plaque rupture and thrombosis (Nabel, 2003).

Hypertension serves as another major cardiovascular risk factor, contributing to vascular remodeling and end-organ damage (Camici & Liberale, 2017b). Chronic elevation of blood pressure accelerates atherosclerosis and increases the workload on the heart, potentially leading to left ventricular hypertrophy and heart failure (Camici & Liberale, 2017b). The interplay between these mechanisms explains the frequent coexistence of coronary artery disease and hypertensive heart disease in clinical practice (Camici & Liberale, 2017b)

Current Interventions and Treatments to Delay Aging

The Role of Stem Cell Regenerative Capacity in Aging

Stem cells gradually lose their regenerative capacity with age due to multiple biological changes. The aging microenvironment disrupts critical signaling pathways that maintain stem cell function (Yun, 2015). This includes accumulated DNA damage, mitochondrial dysfunction, and epigenetic alterations (heritable changes in gene expression that occur without altering the underlying DNA sequence) that impair the cells' ability to self-renew and differentiate (Xu & Jia, 2021). The functional consequences are significant across multiple tissues. Reduced stem cell activity leads to impaired wound healing, diminished tissue repair, and increased vulnerability to age-related diseases (Castellani et al., 2010c). These changes contribute to the progressive decline in organ function observed during aging (Yun, 2015). Current research focuses on reversing these age-related changes through various approaches. Scientists are investigating ways to rejuvenate the stem cell niche and develop epigenetic reprogramming techniques (Ulep et al., 2018a). These interventions aim to restore youthful regenerative capacity and maintain tissue function in aging organisms (Colvin et al., 2017b).

Stem cells hold unique value in aging research due to their dual capacities for self-renewal and tissue regeneration (Goodell & Rando, 2015). However, these capacities decline with age through mechanisms including epigenetic dysregulation (e.g., silencing of pluripotency genes like OCT4 and SOX2; (Ahmed et al., 2017a), mitochondrial dysfunction, and deterioration of the stem cell niche microenvironment (Yun, 2015). Unlike terminally differentiated cells, stem cells serve as reservoirs for tissue repair, and their depletion drives age-related functional decline - for example, reduced hematopoietic stem cell activity leads to immunosenescence (Colvin et al., 2017b), while impaired muscle satellite cell function contributes to sarcopenia. Clinically,

stem cell therapies are already bridging research and medicine: hematopoietic stem cell transplantation (HSCT) treats leukemias while showing potential to rejuvenate aged immune systems; mesenchymal stem cells (MSCs) are used for osteoarthritis and demonstrate anti-inflammatory effects in clinical trials (Di Francesco et al., 2024); and induced pluripotent stem cells (iPSCs) enable personalized therapies like retinal cell implants for macular degeneration (Olah et al., 2020b). Despite challenges including oncogenic risks and high costs, combining stem cell therapies with senolytics or gene editing (e.g., TERT activation) may position them as cornerstones of systemic anti-aging strategies (Yun, 2015).

Stem cell therapy has emerged as a promising approach for combating age-related degeneration and extending lifespan. Recent research demonstrates that transplantation of young stem cells can rejuvenate aged tissues through multiple mechanisms, including direct cell replacement and paracrine signaling (Di Francesco et al., 2024). Mesenchymal stem cells (MSCs) have shown particular potential, as they can modulate the tissue microenvironment by secreting growth factors and anti-inflammatory cytokines that promote regeneration while reducing chronic inflammation associated with aging (Di Francesco et al., 2024). Importantly, studies reveal that stem cell therapies can improve function in multiple aged organ systems simultaneously, addressing the systemic nature of aging rather than targeting single diseases (Di Francesco et al., 2024).

Pharmacological Interventions

Pharmacological interventions for delaying aging have shown promising results in recent research. One of the most studied compounds is rapamycin, an mTOR: a key protein that senses nutrients and energy in cells. When nutrients are abundant, mTOR is active, promoting cell growth, protein production, and metabolism inhibitor that has been shown to extend lifespan in mice by 10-15% while preserving immune function and delaying age-related diseases (Masoro, 2000a). This drug works by targeting the mTOR pathway, which plays a crucial role in cellular metabolism and aging processes. Another important class of drugs are senolytics, such as dasatinib and quercetin, which selectively clear senescent cells that accumulate with age and contribute to tissue dysfunction (Ahmed et al., 2017b). These compounds have demonstrated the ability to improve physical function in aged mice and are now being tested in human clinical trials. NAD+ boosters like nicotinamide mononucleotide (NMN) represent another promising approach, as they enhance mitochondrial function and have shown positive effects in early human trials for improving markers of metabolic health (Goodell & Rando, 2015). These pharmacological strategies work through different mechanisms but share the common goal of targeting fundamental aging processes to extend healthspan. While these interventions show great potential, researchers emphasize the need for further studies to determine optimal dosing regimens and long-term safety profiles in humans (Masoro, 2000b). The development of these anti-aging drugs represents an exciting frontier in medicine, with the potential to treat multiple age-related conditions simultaneously rather than addressing diseases one at a time (Ahmed et al., 2017b). Current evidence suggests that combining different pharmacological approaches with lifestyle interventions may provide the most effective strategy for healthy aging (Goodell & Rando, 2015).

Conclusion

Aging is a multifaceted biological process driven by the gradual accumulation of cellular damage, including genomic instability, mitochondrial dysfunction, and impaired protein homeostasis (Titorenko, 2018d). These molecular alterations contribute to the functional decline of tissues and organs, increasing susceptibility to age-related diseases such as neurodegeneration, cardiovascular disorders, and cancer (Sarkar & Fisher, 2006b). Emerging research highlights the potential of targeted interventions, including senolytics and mitochondrial enhancers, to mitigate age-related pathologies and extend healthspan (Ferrucci et al., 2020).

Moving forward, the translation of aging research into clinical applications remains a critical challenge. Future studies should prioritize the development of reliable biomarkers for biological aging and the validation of therapeutic strategies in human trials (Ferrucci et al., 2020). As the aging population grows, advancing our understanding of these mechanisms will be essential for promoting healthier longevity and reducing the burden of age-associated diseases (Titorenko, 2018e).

References

Ahmed, A. S. I., Sheng, M. H., Wasnik, S., Baylink, D. J., & Lau, K.-H. W. (2017b). Effect of aging on stem cells. World Journal of Experimental Medicine, 7(1), 1–10. https://doi.org/10.5493/wjem.v7.i1.1

Boveris, A., & Navarro, A. (2008). Brain mitochondrial dysfunction in aging. IUBMB Life, 60(5), 308–314. https://doi.org/10.1002/iub.46

Camici, G. G., & Liberale, L. (2017a). Aging: The next cardiovascular disease? European Heart Journal, 38(21), 1621–1623. https://doi.org/10.1093/eurheartj/ehx239

Castellani, R. J., Rolston, R. K., & Smith, M. A. (2010c). Alzheimer Disease. Disease-a-Month, 56(9), 484–546. https://doi.org/10.1016/j.disamonth.2010.06.001

Colvin, M. M., Smith, C. A., Tullius, S. G., & Goldstein, D. R. (2017a). Aging and the immune response to organ transplantation. The Journal of Clinical Investigation, 127(7), 2523–2529. https://doi.org/10.1172/JCI90601

Di Francesco, A., Deighan, A. G., Litichevskiy, L., Chen, Z., Luciano, A., Robinson, L., Garland, G., Donato, H., Vincent, M., Schott, W., Wright, K. M., Raj, A., Prateek, G. V., Mullis, M., Hill, W. G., Zeidel, M. L., Peters, L. L., Harding, F., Botstein, D., … Churchill, G. A. (2024). Dietary restriction impacts health and lifespan of genetically diverse mice. Nature, 634(8034), 684–692. https://doi.org/10.1038/s41586-024-08026-3

DiLoreto, R., & Murphy, C. T. (2015). The cell biology of aging. Molecular Biology of the Cell, 26(25), 4524–4531. https://doi.org/10.1091/mbc.E14-06-1084

Ferrucci, L., Gonzalez-Freire, M., Fabbri, E., Simonsick, E., Tanaka, T., Moore, Z., Salimi, S., Sierra, F., & de Cabo, R. (2020). Measuring biological aging in humans: A quest. Aging Cell, 19(2), e13080. https://doi.org/10.1111/acel.13080

Fibroblasts: Advances in Inflammation, Autoimmunity and Cancer. (2021b). BoD – Books on Demand.

Gensler, H. L., & Bernstein, H. (1981b). DNA Damage as the Primary Cause of Aging. The Quarterly Review of Biology, 56(3), 279–303. https://doi.org/10.1086/412317

Goodell, M. A., & Rando, T. A. (2015). Stem cells and healthy aging. Science, 350(6265), 1199–1204. https://doi.org/10.1126/science.aab3388

Iqbal, K., Del C. Alonso, A., Chen, S., Chohan, M. O., El-Akkad, E., Gong, C.-X., Khatoon, S., Li, B., Liu, F., Rahman, A., Tanimukai, H., & Grundke-Iqbal, I. (2005). Tau pathology in Alzheimer disease and other tauopathies. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1739(2–3), 198–210. https://doi.org/10.1016/j.bbadis.2004.09.008

Jeyapalan, J. C., & Sedivy, J. M. (2008). Cellular senescence and organismal aging. Mechanisms of Ageing and Development, 129(7–8), 467–474. https://doi.org/10.1016/j.mad.2008.04.001

Knopman, D. S., Amieva, H., Petersen, R. C., Chételat, G., Holtzman, D. M., Hyman, B. T., Nixon, R. A., & Jones, D. T. (2021a). Alzheimer disease. Nature Reviews Disease Primers, 7(1), 33. https://doi.org/10.1038/s41572-021-00269-y

Masoro, E. J. (2000b). Caloric restriction and aging: An update. Experimental Gerontology, 35(3), 299–305. https://doi.org/10.1016/S0531-5565(00)00084-X

McGuire, P. J. (2019). Mitochondrial Dysfunction and the Aging Immune System. Biology, 8(2), Article 2. https://doi.org/10.3390/biology8020026

Miwa, S., Kashyap, S., Chini, E., & Zglinicki, T. von. (2022). Mitochondrial dysfunction in cell senescence and aging. The Journal of Clinical Investigation, 132(13). https://doi.org/10.1172/JCI158447

Nabel, E. G. (2003). Cardiovascular Disease. New England Journal of Medicine, 349(1), 60–72. https://doi.org/10.1056/NEJMra035098

Noto, S. (2023). Perspectives on Aging and Quality of Life. Healthcare, 11(15), Article 15. https://doi.org/10.3390/healthcare11152131

Olah, M., Menon, V., Habib, N., Taga, M. F., Ma, Y., Yung, C. J., Cimpean, M., Khairallah, A., Coronas-Samano, G., Sankowski, R., Grün, D., Kroshilina, A. A., Dionne, D., Sarkis, R. A., Cosgrove, G. R., Helgager, J., Golden, J. A., Pennell, P. B., Prinz, M., … De Jager, P. L. (2020a). Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. Nature Communications, 11(1), 6129. https://doi.org/10.1038/s41467-020-19737-2

Richter, T., & Zglinicki, T. V. (2007b). A continuous correlation between oxidative stress and telomere shortening in fibroblasts. Experimental Gerontology, 42(11), 1039–1042. https://doi.org/10.1016/j.exger.2007.08.005

Sarkar, D., & Fisher, P. B. (2006b). Molecular mechanisms of aging-associated inflammation. Cancer Letters, 236(1), 13–23. https://doi.org/10.1016/j.canlet.2005.04.009

Schumacher, B., Pothof, J., Vijg, J., & Hoeijmakers, J. H. J. (2021). The central role of DNA damage in the ageing process. Nature, 592(7856), 695–703. https://doi.org/10.1038/s41586-021-03307-7

Sengoku, R. (2020). Aging and Alzheimer's disease pathology. Neuropathology, 40(1), 22–29. https://doi.org/10.1111/neup.12626

Shapiro, E., Biezuner, T., & Linnarsson, S. (2013). Single-cell sequencing-based technologies will revolutionize whole-organism science. Nature Reviews Genetics, 14(9), 618–630. https://doi.org/10.1038/nrg3542

Sies, H., Berndt, C., & Jones, D. P. (2017). Oxidative Stress. Annual Review of Biochemistry, 86(Volume 86, 2017), 715–748. https://doi.org/10.1146/annurev-biochem-061516-045037

Titorenko, V. I. (2018a). Molecular and Cellular Mechanisms of Aging and Age-related Disorders. International Journal of Molecular Sciences, 19(7), Article 7. https://doi.org/10.3390/ijms19072049

Trifunovic, A., & Larsson, N.-G. (2008c). Mitochondrial dysfunction as a cause of ageing. Journal of Internal Medicine, 263(2), 167–178. https://doi.org/10.1111/j.1365-2796.2007.01905.x

Ulep, M. G., Saraon, S. K., & McLea, S. (2018a). Alzheimer Disease. The Journal for Nurse Practitioners, 14(3), 129–135. https://doi.org/10.1016/j.nurpra.2017.10.014

Wang, M., Song, W., Ming, C., Wang, Q., Zhou, X., Xu, P., Krek, A., Yoon, Y., Ho, L., Orr, M. E., Yuan, G.-C., & Zhang, B. (2022b). Guidelines for bioinformatics of single-cell sequencing data analysis in Alzheimer's disease: Review, recommendation, implementation and application. Molecular Neurodegeneration, 17(1), 17. https://doi.org/10.1186/s13024-022-00517-z

Xu, H., & Jia, J. (2021). Single-Cell RNA Sequencing of Peripheral Blood Reveals Immune Cell Signatures in Alzheimer's Disease. Frontiers in Immunology, 12. https://doi.org/10.3389/fimmu.2021.645666

Yamada-Fukunaga, T., Yamada, M., Hamatani, T., Chikazawa, N., Ogawa, S., Akutsu, H., Miura, T., Miyado, K., Tarín, J. J., Kuji, N., Umezawa, A., & Yoshimura, Y. (2013). Age-associated telomere shortening in mouse oocytes. Reproductive Biology and Endocrinology, 11(1), 108. https://doi.org/10.1186/1477-7827-11-108

Yousefzadeh, M., Henpita, C., Vyas, R., Soto-Palma, C., Robbins, P., & Niedernhofer, L. (2021). DNA damage—How and why we age? eLife, 10, e62852. https://doi.org/10.7554/eLife.62852

Yun, M. H. (2015). Changes in Regenerative Capacity through Lifespan. International Journal of Molecular Sciences, 16(10), Article 10. https://doi.org/10.3390/ijms161025392