Egypt. J. Chem. Vol. 68, No: 12, pp. **21 - 27**(2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Biochemical Pathways in Aging and Longevity: Review of Mechanisms and Therapeutic Implications

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Abstract

Aging is a complex, universal biological process involving gradual degradation of function across all organ systems, driven by the growing molecular and cellular damage from a variety of stressors. This review connects recent advances in the molecular, cellular, and systemic aspects of aging and their central role in the pathogenesis of age-related diseases like Alzheimer's disease (AD), Parkinson's disease (PD), heart failure (HF), atherosclerosis, type 2 diabetes mellitus (T2DM), and nonalcoholic fatty liver disease (NAFLD). The principal molecular signatures of aging—genomic instability, telomere loss, epigenetic reprogramming, loss of proteostasis, autophagy impairment, mitochondrial dysfunction, and altered nutrient sensing—are covered in some detail. Cell processes, such as senescence and stem cell depletion, and systemic processes, such as hyperactive intercellular communication, are considered as well. Mechanistic crosstalk and disease inception are described, with new approaches, such as senolytics, gene therapy, and lifestyle intervention, with which to target aging and with it its accompanying pathologies. By integrating advances from high-throughput omics approaches and promising latest advances in therapeutics, this manuscript represents the primary unifying framework for advancing understanding of aging and improving the translation of longevity-promoting interventions.

Keywords: cellular senescence, aging, genomic instability, age-related diseases, therapeutic intervention

1. Introduction

Aging is a multifaceted biological progression involving progressive, non-reversible impairment of all of the body's systems, as a result of cumulative damage at the cellular and molecular levels over the lifespan from a broad spectrum of stressors (Kirkwood, 2005). Such impairment makes people extremely susceptible to chronic disease, including AD, PD, cardiovascular disease, T2DM, and NAFLD, with total healthcare expenditure placing enormous burdens on healthcare systems globally (López-Otín et al., 2013). Seminal studies, such as demonstrating in a 1925 experiment that the duration of light impacts the lifespan and growth rate of Drosophila melanogaster, triggered scientific curiosity regarding the plasticity of aging (Pearl, 1925). In later studies, it has been shown that CR promotes longevity and delays age-related disease in mice, illustrating the plasticity of aging processes as long ago as (McCay et al., 1989). Approximately 30 years ago, the identification of a long-lived Caenorhabditis elegans strain proved revolutionary in identifying genetic determinants of longevity, in addition to opening new avenues of aging research (Kenyon et al., 1993).

Aging is now recognized as one of the primary determinants for most chronic diseases, with comorbidities becoming a standard after age 60 and involving multifaceted, interdependent treatment regimens (Jaul & Barron, 2017). To understand the complicated interplay between aging and disease, it is important to recognize its origins in order to identify potential points of intervention and new opportunities to achieve healthful longevity. Cellular senescence is a hallmark of aging, characterized by the gradual cessation of cell growth, differentiation, and function, ultimately causing damage to tissue homeostasis and leading to pathological conditions related to aging (Harman, 1956; Hayflick & Moorhead, 1961). In 1956, Harman formulated the free radical hypothesis of aging, which stated that oxidative damage caused by reactive oxygen species (ROSs) caused degenerative changes (Harman, 1956). Over time, telomere dysfunction, loss of proteostasis, epigenetic alterations, and mitochondrial dysfunction have emerged as the major causes of aging (López-Otín et al., 2013).

The review gives an overall impression of the most current advances in the molecular, cellular, and systemic biology of aging. The review emphasizes the pivotal positions of these processes in disease pathogenesis of aging and the possibilities for pharmacologic, genetic, and lifestyle interventions in slowing down aging and disease processes.

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Receive Date: 5 February 2025, Revise Date: 11 June 2025, Accept Date: 12 June 2025
DOI: 10.21608/ejchem.2025.363561.11363

1. Molecular Mechanisms of Aging

Nine hallmarks of aging were described by López-Otín et al. (2013) in 2013: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, impaired regulation of nutrients, mitochondrial defects, cellular senescence, stem cell exhaustion, and altered cell-to-cell communication. Other works have added malfunctioning autophagy as the tenth hallmark, which suggests its importance in cellular homeostasis (Partridge & Kroemer, 2013). The processes are outlined more fully below (Figure 1).

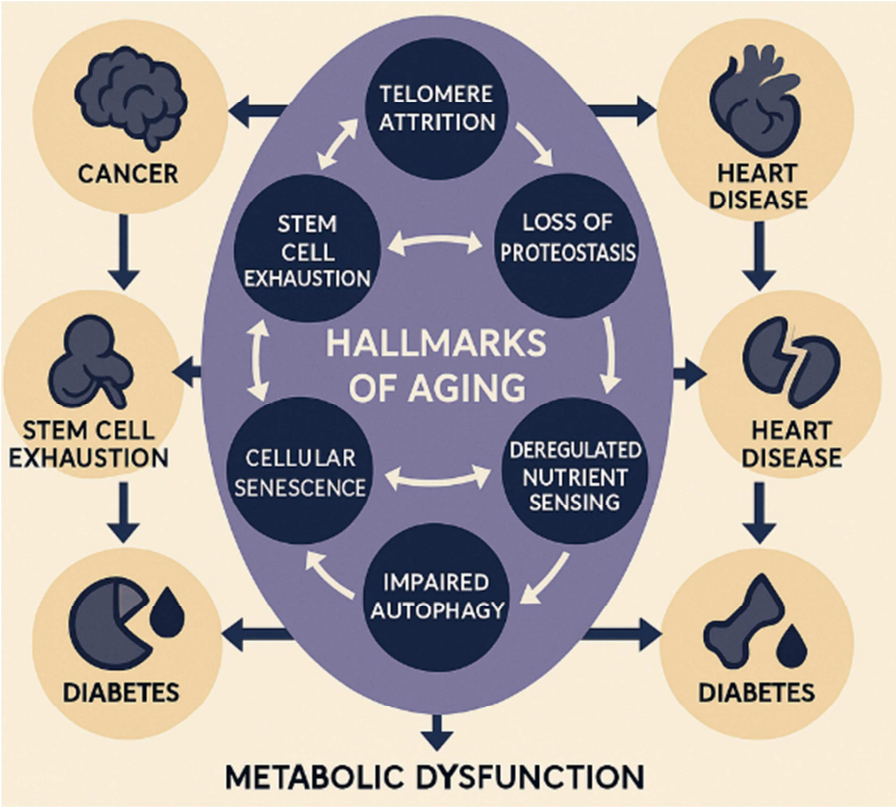

Figure 1: Hallmarks of aging and their interconnections.

Genomic instability, one of the major determinants of aging, is caused by DNA damage accumulation resulting in gene expression dysregulation, impaired function of cells, and cell death (Vijg & Suh, 2013). Endogenous DNA damage in terms of double-strand breaks initiates mechanisms of DNA damage response, such as p53-p21 and p16INK4a-pRb, that bring about cell cycle arrest for prevention of transmission of deleterious gene information (Campisi, 2013). Single-cell RNA sequencing of over 350,000 cells of six groups of C57BL/6JN mice (ages 1-30 months) proved the direct correlation of aging with genomic mutation in 23 tissues, with the bladder and tongue showing the greatest rates of mutation (Tabula Muris Consortium, 2020). Notably, there are lower somatic as well as germline mutations in centenarians, indicating more effective mechanisms of DNA repair coupled with maintenance of genomic stability (Cawthon et al., 2020).

Chronic DNA damage foci in senescent cells induce DNA segments with senescence-enforcing chromatin modifications (DNA-SCARS), dynamic complexes that regulate growth arrest and senescence-associated secretory phenotype (SASP), such as pro-inflammatory cytokines, chemokines, and growth factors (Rodier et al.). Disruption of nuclear envelope protein Lamin B1 destabilizes the envelope, with release of cytoplasmic chromatin fragments (CCFs) identified as cyclic GMP-AMP synthase (cGAS) receptors, catalyzing cycling of cyclic GMP-AMP (cGAMP). This activates stimulator of interferon genes (STING), triggering SASP-mediated tissue inflammation (Dou et al., 2017). Mitochondrial DNA (mtDNA) lacking histone protection and functional DNA mechanisms is eminently prone to mutation by spatial proximity with the generated ROS in the respiratory chain (Wallace, 1982). Aging tissue contains reduced mtDNA copy number and increased mutation rate, with oxidative stress fostering mtDNA leakage, further triggering cGAS-STING and SASP (Sliter et al., 2018). Circulating cell-free mtDNA in body fluid is a novel inter-tissue communication signal, evidenced in neuropsychiatric disorders and systemic inflammation (West et al., 2015). A recent study revealed that melatonin deficiency, age-related decline, disrupts mitochondrial homeostasis, increasing mtDNA release and inflammation in Huntington's disease mice, ameliorated with melatonin supplementation (Hardeland, 2018).

Mutations in the Lamin A/C (LMNA) gene, modifying nuclear structure, result in aging diseases like HGPS, neuropathies, and muscular dystrophy (Eriksson et al., 2003). Reduced Lamin B1 with age in humans causes disruption of neural stem cell division, but its replacement enhances mouse neurogenesis (Jessberger et al., 2014). Endogenous cytoplasmic

DNA initiates aseptic inflammation, activating KU complex (Ku70/Ku80) and mTOR pathways, and triggering CD4+ T-cell proliferation and autoimmunity with age (Lan et al., 2019). Iterative "junk DNA" tandem repeats, comprising ~50% of the human genome, influence aging. For instance, VNTR2-1 enhances telomerase activity, with longer tandem repeats being linked with longer telomeres but with increased cancer risk, suggesting involvement of genetic variation in aging (Kang et al., 2018).

Telomeres, repetitive TTAGGG motifs of the chromosome ends, maintain genome stability through interaction with the shelterin complex (Blackburn, 2005). Gradual shortening with cell division for attainment of the Hayflick limit triggers DNA damage responses, senescence, and expression of proinflammatory factors (von Zglinicki, 2002). The enzyme telomerase, a reverse transcriptase, extends telomeres of embryonic stem cells and immune cells but declines with age (Greider & Blackburn, 1985). Telomerase reactivation in aged cells mitigates damage, as in HGPS mice, where overexpression of telomerase mRNA lowered inflammation, DNA damage, and extended lifespan (Bär et al., 2014). Telomerase is overexpressed in ~90% of cancers, however, and is a barrier for anti-aging treatment (Shay & Wright, 2019). Intra-person variation of telomere length is extremely large for persons of the same age and is controlled by environmental as well as genetic elements, with shorter telomeres linked with premature aging and disease susceptibility (Armanios, 2013).

Epigenetic regulation of gene expression (Pal & Tyler, 2016) is driven by DNA methylation, histone modifications, chromatin remodeling, and ncRNA function, without changing the DNA sequence itself. Cytosine methylation (5mC) and hydroxymethylcytosine methylation (5hmC) are the central epigenetic markers that repress or activate gene expression (Cruickshanks et al., 2013). In essence, epigenetic drift with aging is composed of hypomethylation of repeated elements in heterochromatin and hypermethylation of promoter-CpG islands that leads to disruption of gene regulation (Horvath, 2013). Epigenetic clocks including Horvath's (2013) and Levine's DNAm PhenoAge (2018), define biological age and risk of disease based on methylation patterns and have been explored in contexts including dementia and NAFLD (Levine et al., 2018; Shireby et al., 2020). Epigenetic aging is delayed through lifestyle intervention, like improved diet, demonstrated in the DAMA study (Quach et al., 2017).

Chromatin structure is determined by histone modification (acetylation, methylation, phosphorylation). For example, methylation of H3K4, H3K36, or H3K79 induces transcription, while methylation of H3K27 or H4K20 represses transcription, and their corresponding changes are associated with premature aging syndrome, like HGPS and Werner syndrome (Sarg et al., 2015). Histone acetylation by acetyltransferases promotes transcription, and deacetylases repress transcription, and deacetylase malfunction shortens yeast lifespan (Dang et al., 2009). Chromatin remodeling by ATP-dependent enzymes like SWI2/SNF2 makes new combinations of nucleosome occupancy, where the aged cells are more accessible and disorganized (O'Sullivan & Karlseder, 2012; Liu et al., 2020). Impaired histone acetylation and chromatin condensation due to a loss of acetyl-CoA in C. elegans arise from mitochondrial stress (Liu et al., 2020). Non-coding RNA (ncRNA) regulates aging. Reduction in exosomal miRNAs has been documented in aging brains, with senescent circRNA becoming abundant in females, potentially due to increased stability (Zhang et al., 2019; Xu et al., 2021).

Proteostasis, the process of regulation of protein synthesis, folding, and breakdown, declines with age and causes neurodegenerative diseases such as AD and Huntington’s disease (Hipp et al., 2019). Chaperones, such as heat shock proteins, also have a role in preventing misfolding and misassembly, while the endoplasmic reticulum's response to unfolded proteins gets rid of misfolded molecules by either the ubiquitin-proteasome system (UPS), or the autophagy-lysosomal pathway (Hetz et al. 2019). If UPR, UPS, or autophagy fails misfolded proteins will aggregate or cluster and activating transcription factors (ATF3, ATF4) serve important roles in this process (Klaips et al. 2018, Wang et al. 2020). Insulin-like growth factor-1 (IGF-1) promotes protein synthesis through the PI3K/Akt/mTOR pathway but also results in aging. Therefore, inhibiting IGF-1 or inactivating the PI3K/Akt/mTOR pathway will prolong life span in model organisms, including worms and flies (Kenyon 2010). The small ubiquitin-like modifier (SUMO) appears to stabilize proteins, and mounting evidence suggests that the control of SUMO regulates longevity in C. elegans (Srivastava et al. 2021). Translation pause induction during aging by ribosomes overburdens quality control, facilitating aggregation (Stein et al., 2022).

Autophagy, which removes non-functional organelles and aggregates, is distinctly regulated through all stages of the lytic process to maintain cellular homeostasis (Figure 2). Autophagy declines with age, and so does the ability to maintain intracellular homeostasis and proper cellular function (Rubinsztein et al. 2011). Autophagy can be initiated through the inhibition of mTOR or the activation of AMPK. The regulation of ATG5, ATG7, and BECN1 genes during natural aging has been shown to increase mimicked aging in human neurons (Mizushima & Komatsu, 2011; Lipinski et al., 2010). Enhanced autophagy, such as overexpressing ATG-1, ATG-7, and ATG-18 in *C. elegans*, retards aging (Partridge & Kroemer, 2013). Transition metal (iron, copper) deposition in cells with age inhibits autophagic degradation, inducing ferroptosis and degenerative disease (Masaldan et al., 2019). Mitophagy, removing damaged mitochondria, is disrupted in aging, increasing oxidative stress (Palikaras et al., 2018).

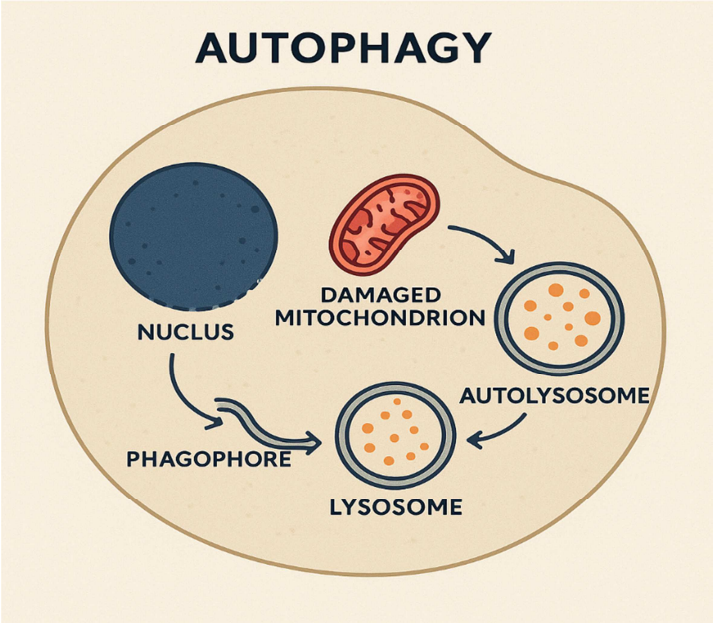

Figure 2: Autophagy mechanisms.

2. Mitochondrial Dysfunction

Mitochondrial dysfunction is proposed as the convergence point for aging and is implicated mainly by mtDNA mutation, and resultant reactive oxygen species (ROS) production, impairing metabolism and promoting aging (Sun et al., 2016). Mitochondrial DNA mtDNA carries a high mutation load, has no active repair system, accumulates mutations, has a small copy number, and its design compromises function (Wallace, 2010). Oxidative stress from respiratory-chain electron leakage further incentivizes mtDNA damage, with leaked mtDNA activating cGAS-STING and inflammation (Sliter et al., 2018). Mitochondrial ferritin accumulation initiates mitophagy but its malfunction induces senescence (Wang et al., 2021). Melatonin deficiency amplifies mitochondrial dysfunction, with increasing inflammation, as noted in Huntington's Disease (Hardeland, 2018).

Nutrient-sensing pathways, including the insulin/IGF-1 pathway, the mTOR pathway, and AMPK, may regulate metabolism and aging (Barzilai et al., 2012). When nutrients stimulate the insulin/IGF-1 pathway, it promotes anabolism by activating the downstream mTORC1 pathway via the PI3K/Akt pathway, ultimately leading to the phosphorylation of TSC1/TSC2 proteins, which regulate mTORC1. When mTORC1 is activated, it promotes protein synthesis and inhibits autophagy (Johnson et al., 2013). If nutrients are not available, AMPK will become activated due to low energy status (high AMP to ATP ratio) and inhibit mTORC1, which would promote catabolism (Houtkooper et al., 2011). Dysregulation of the nutrient-sensing pathways, as seen in the case of insulin resistance, speeds up the aging process, as well as diseases such as type 2 diabetes mellitus (Barzilai et al., 2012). The gut microbiota is involved in nutrient sensing through modulation of the gut-brain axis, and when we have dysbiosis, especially during aging, there will be increased inflammation in addition to neurodegeneration (Cryan & Dinan, 2012). Centenarians' unique microbiota, with high secondary bile acid-producing bacteria, promotes longevity (Biagi et al., 2016).

3. Cellular Mechanisms of Aging

Senescence, which is a permanent arrest of the cell cycle, impedes tissue homeostasis and leads to aging through a senescence-associated secretory phenotype (SASP), which leads to the secretion of pro-inflammatory cytokines, chemokines, and growth factors (van Deursen, 2014). The SASP results in chronic inflammation, a loss of regeneration, and contributes to age-related disease (Copland et al., 2014; Demaria et al., 2014). Tissue senescence markers such as p16INK4a, p21, and SA-β-gal accumulate with age, and senescent cells accumulate in aged tissue, particularly organs like the liver and heart (Krishnamurthy et al., 2004). The cGAS-STING pathway is activated through DNA damage, resulting in a SASP that further damages tissue (Dou et al., 2017).

Stem cell depletion or loss of regeneration capacity is induced by DNA damage, senescence, and epigenetic modifications (Rossi et al., 2008). Defective neural stem cell proliferation reduces the strength of neurogenesis, while recovery of Lamin B1 restores stem cell function in aged mice (Jessberger et al., 2014). Disruption of hematopoietic stem cells reduces immune strength, resulting in immunosenescence, evidenced by impaired adaptive immunity and chronic inflammation (Geiger et al., 2013).

Altered intercellular communication, via SASP and inflammation signals, disrupts tissue homeostasis (Franceschi & Campisi, 2014). Inflammatory signals stimulated by cGAS-STING disable clearance and heighten dysfunction (Dou et al., 2017). Aberrant exosomal miRNA signaling decreases tissue repair, accelerating aging (Zhang et al., 2019). Systemic inflammation driven by gut microbiota dysbiosis enhances neurodegenerative and metabolic disease (Cryan & Dinan, 2012).

4. Pathogenic processes in age-related disease

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by neuronal death, amyloid-β (Aβ) plaques, and tau neurofibrillary tangles that disrupt cognition and memory (Selkoe & Hardy, 2016). The accumulation of DNA damage due to substandard repair, results in increased oxidative stress and inflammation contributing to neurodegeneration (Madabhushi et al., 2014). Meanwhile, epigenetic modifications that, for example, include DNA methylation and histone modification (e.g., H3 phosphorylation, H4 deacetylation), result in abnormal regulation of gene activity in AD neurons (De Jager et al., 2014). Aβ aggregation uses dependent plasticity, and mitochondrial/functional disruption that generates reactive oxygen species (ROS) and disturbs neuronal homeostasis (Bloom, 2014). Hyperphosphorylated tau creates neurofibrils and increases maladaptive neuronal activity (Bloom, 2014). Dysfunctional mitophagy accumulates damaged mitochondria, reducing ATP and augmenting Aβ and tau pathologies (Kerr et al., 2017). Senescent astrocytes secrete SASP, promoting Aβ, tau, and neuroinflammation, and impairing synaptic plasticity and blood-brain barrier function (Bhat et al., 2012).

Parkinson's Disease (PD) is a movement disorder caused by the loss of dopaminergic neurons and aggregation of α-synuclein into Lewy bodies, resulting in dyskinesias (Poewe et al., 2017). α-Synuclein oligomers are able to spread from cell to cell, probably through a mechanism involving lymphocyte-activation gene 3 (LAG3), further worsening neurodegeneration (Luk et al., 2012; Mao et al., 2016). Genetic mutations in SNCA, PINK1, LRRK2, and GBA increase the risk of developing PD (Singleton et al., 2013). Neuroinflammation, specifically through senescent cells and the senescence-associated secretory phenotype (SASP), can also increase IL-6 and IL-1β, as well as implicating the α-synucleinopathy in the further downstream mechanisms of TLR2 and NLRP3 activation (McGeer et al., 2001; Zhang et al., 2020a). There are Drugs being developed called disease-modifying therapies that target α-synuclein aggregation in order to restore the normal dopamine levels (Athauda & Foltynie, 2015).

Heart failure (HF) affects more than 64 million people globally and is induced through senescent cardiomyocyte accumulation and aging of cardiac cells, resulting in loss of contractility and impaired energetics (Groenewegen et al., 2020). Increased oxidative stress and mitochondrial dysfunction can lead to the overproduction of reactive oxygen species (ROS), resulting in increased DNA damage, lipid peroxidation, and cellular senescence (Tsutsui et al., 2011). Senescent cardiomyocytes also secrete a senescence-associated secretory phenotype (SASP) that can induce inflammation, senescence, and fibrosis in neighboring cells (Anderson et al., 2019). Epigenetic alterations, such as KDM4D overexpression, promote proliferation but could potentially drive aging (Zhang et al., 2020b). Non-myocyte senescence of endothelial cells provokes HF through vascular dysfunction and atrial fibrillation (Zhu et al., 2016). Chemotherapeutic agents, anthracyclines, induce senescence due to DNA and mitochondrial injury, which exacerbate HF (Zhang et al., 2017).

Atherosclerosis, a result of vascular aging, is characterized by senescent endothelial and vascular smooth muscle cells (VSMCs) which inhibit vasodilation and promote inflammation (Wang & Bennett, 2012). Metabolic dysfunction resulting from oxidative stress through defective Nrf2 triggers endothelial injury, increasing ROS, and decreasing nitric oxide (Ungvari et al., 2018). In addition, micro-RNAs (miRs), such as miR-217, interact indirectly with SIRT1, leading to downregulation of SIRT1 and resulting in senescence (Menghini et al., 2014). Senescent VSMCs release cytokines (e.g., CCL2, IL-6) that attract monocytes and promote plaque growth (Goronzy & Weyand, 2016). Immune senescence, with increased Th17 and reduced regulatory T cells, reinforces autoimmunity, while impaired endothelial progenitor cells (EPCs) compromise repair (Xu et al., 2007).

Type 2 Diabetes Mellitus (T2DM) in older adults also has a compounding quality of aging β-cells and the risk factor for insulin resistance complicating glucose and lipid homeostasis (Palmer et al., 2019). This condition is compounded when telomeres shorten, and which leads to suppression of β-cell replication and insulin being released; notably during the overexpression of p16INK4a in pancreatic islets (Kuhlow et al., 2008). Increased levels of oxidative stress and inflammation via TLR4-MyD88 create IL-1β, IL-6, and CCL2, further biasing altered β-cell function and enhancing macrophage infiltration (Eguchi et al., 2012). Furthermore, the senescence-associated secretory phenotype (SASP) is part of cellular senescence and will induce paracrine senescence (Minamino et al., 2009).

Non-alcoholic Fatty Liver Disease (NAFLD) is a chronic liver disease including a spectrum from excess fat within hepatocytes leading to non-alcoholic steatohepatitis (NASH) in 10-25% of patients (Younossi et al., 2018). Genetic single-nucleotide polymorphisms (SNPs), including the PNPLA3 rs738409 polymorphism, are an independent risk factor for incident NAFLD, and the presence of epigenetic methylation is associated with fibrosis (Romeo et al., 2008; Loomba et al., 2018). Mitochondrial dysfunction leads to a reduction in fatty acid β-oxidation, as lipid accumulation takes place, and reactive oxygen species (ROS) magnify the damage (Sunny et al., 2017). Endoplasmic reticulum (ER) stress has altered Ca2+ homeostasis, which leads to the activation of IRE1α and PERK pathways involving inflammation and apoptosis (Yang et al., 2014). Impaired lipophagy and mitophagy lead to lipid accumulation with dysfunctional mitochondria, which worsens NASH (Ogrodnik et al., 2017). Senescent hepatocytes, expressing p16 and p53, impair regeneration, associated with NAFLD progression (Ogrodnik et al., 2017). Gut microbiota dysbiosis and insulin resistance increase inflammation via TLRs and NLRs (Schwabe & Jobin, 2013).

5. Interventions and Future Directions

Anti-aging interventions are designed to slow aging and delay the occurrence of disease by also preventing it through lifestyle, pharmacologic, and inventive interventions. Lifestyle interventions such as caloric restriction (CR) and exercise have been shown to improve mitochondrial activity, improve autophagic mechanisms, and decrease oxidative stress (López-Lluch & Navas, 2016). Additionally, senolytic agents dasatinib and quercetin selectively induce senescent cell death, mitigate complications of diabetes, and improve tissue function (Palmer et al., 2021). Gene therapies like telomerase activation prolong life in animal models, but cancer risks require caution (Bär et al., 2014). Stem cell therapy restores regenerative ability, though clinical usefulness is blighted by complications like immune rejection (Nguyen et al., 2019). Drug delivery through nanotechnology and RNA therapies offers targeted strategies for age-related disease (Wang et al., 2023).

Other strategies, like traditional Chinese medicine and acupuncture, can slow down aging symptoms but do not have significant clinical evidence (Li et al., 2020). High-throughput omic tools like single-cell transcriptomics, proteomics, and metabolomics enable extensive aging profiling with intervention discovery of biomarkers (Johnson et al., 2022). Artificial intelligence (AI) enables drug discovery via aging pathway identifications, treatment efficacy prediction, and reduced treatment regimens (Zhang et al., 2023). Guaranteeing long-term safety, reducing socioeconomic disparities, and long-term outcome verification through large clinical trials are challenging (Cummings et al., 2023). Future research should focus more on multi-target interventions like epigenetic modulators, senolytics, and regenerative medicine in addressing the complexity of aging.

6. Conclusion

Ageing is a multifaceted process with molecular, cellular, systemic, and environmental mechanisms, with environmental and sociological determinants. Understanding these mechanisms has identified new targets for ageing diseases from AD to NAFLD. Convergence of omics, novel therapeutics, new treatments, and prevention will drive personalized approaches for healthy ageing against global health problems from ageing populations. Interdisciplinary research and strict clinical validation will drive these findings into effective therapies, improving longevity and reducing disease burden.

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