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Review Article

Molecular mechanisms of physiological aging: hallmarks, environmental impacts, and pathways to healthy longevity

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ABSTRACT

Aging is a multifaceted biological process shaped by intrinsic molecular mechanisms and extrinsic environmental factors, culminating in systemic functional decline and heightened vulnerability to age-related diseases. This review explores the hallmarks of physiological aging, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, cellular senescence, chronic inflammation, and gut dysbiosis. These interconnected pathways drive the gradual deterioration of cellular and tissue function, underpinning both natural aging and the onset of pathologies such as neurodegeneration, cardiovascular disease, and cancer. Environmental toxins including mycotoxins, heavy metals, chemical clastogens, and pollutants exacerbate aging by inducing oxidative stress, disrupting DNA repair, and altering epigenetic regulation, thereby accelerating cellular damage and systemic dysfunction. We highlight the role of mitochondrial dysfunction in senescence, the dual nature of autophagy in proteostasis, and the inflammatory cascade triggered by senescent cells, which perpetuates tissue degeneration. Furthermore, dysbiosis of the gut microbiota emerges as a critical modulator of aging, linking microbial imbalance to metabolic and immune dysregulation. By synthesizing current insights into these mechanisms, this review underscores the importance of targeting aging hallmarks to develop interventions that promote healthy longevity. Strategies such as dietary modulation, proteasome activation, and probiotic therapies demonstrate potential in mitigating age-related decline. Understanding the interplay between molecular pathways and environmental stressors offers a roadmap for innovative therapies aimed at decelerating aging processes, enhancing health span and reducing the burden of age-associated diseases. This holistic perspective bridges fundamental aging biology with translational applications, emphasizing the urgency of interdisciplinary approaches to address the challenges of global population aging.

1. INTRODUCTION

Significant advancements have been made in the study of aging and senescence within the last 20 years. We must first set aside any assumptions about how aging manifests itself to examine the systems biology of aging. Does the skin have wrinkles? Disoriented memory? Tense joints? Despite the fact that these are some of the characteristics we may connect with aging, the systems biology approach to aging focuses more on the reasons behind the coordinated, time-dependent biological changes that take place across numerous systems. For instance, how a once-healthy person may get aged skin, hazy memory, and tight joints all at the same time (McCormick & Promislow, 2018; López-Otín et al., 2023). Age is a time-dependent deterioration in physiological organ function that is unavoidable and ultimately results in death. An important risk factor for the most prevalent illnesses, including diabetes, cancer, heart disease, and Alzheimer's disease, is age (Kaeberlein, 2013; Li et al., 2021). Every living thing is always battling both internal and external threats that could harm it. Living things' lives would be very short without their repair systems because the buildup of toxic substances and chemicals such as heavy metals, mycotoxins, and environmental pollutants would impair the cellular components and their ability to operate, which would ultimately cause damage to the

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different tissues and hasten the aging process of the entire organism (López-Otín et al., 2013). The field of geroscience, which examines the relationship between aging physiology and the emergence of chronic diseases linked to aging, offers a theoretical and practical framework for organizing existing knowledge in an organized manner and planning future research directions. In order to develop interventions that prevent or slow the beginning and advancement of the mechanisms causing age-related diseases, geroscience has sought to understand the aging processes at all of its levels (genetic, molecular, cellular, etc.) (Anton et al., 2020; Kennedy et al., 2014). As people age, their body tissues and organs deteriorate or decline in function, making them more vulnerable to age-related illnesses and reducing the amount of time they may live a healthy life (Zhang et al., 2022; Li et al., 2024).

2. HALLMARKS OF AGING

The progressive degenerative state of aging might have both physiological and pathological components (Aunan et al., 2016; Sacco, et al., *2021*; Aguilar-Hernández et al., 2023). Degenerative processes such as telomere attrition (López-Otín et al., 2023), DNA damage (Stead and Bjedov, 2021; Zhao et al., 2023), mitochondrial dysfunction (Zhao et al., 2020; Yang et al., 2024), impaired macro-autophagy (Kaushik et al., 2021; Cassidy and Narita, 2022), stem cell exhaustion, inflammation (Kalamakis et al., 2019; Schneider et al., 2021), deregulated nutrient-sensing (Slack et al., 2015), altered intercellular communication (Villeda et al., 2011; Fafián-Labora and O'Loghlen, 2020; Yang et al., 2021), and dysbiosis (DeJong, Surette and Bowdish, 2020; Alsegiani and Shah, 2022) are all part of physiological aging (Fig. 1), which happens after maturation and results in decline in systemic function. It's important to note that these improvements are participatory and decentralized rather than stand alone. Diabetes, Parkinson's disease, Alzheimer's disease, cancer, degenerative joint disease, cardiovascular disease, and cerebrovascular disease are some of the extrinsic variables that contribute to pathological aging, which includes senile pathological aging alterations.

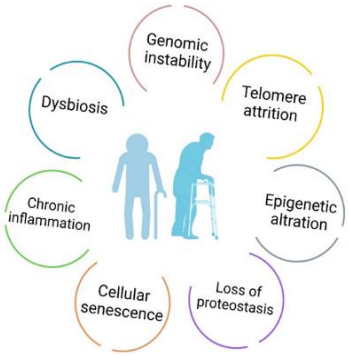

Fig. 1**.** Hallmarks of aging

2.1. Genomic instability

The genome is continuously exposed to intracellular and extracellular damage sources including environmental toxins and chemicals, which necessitate the use of genetic material repair processes to stop the damage from piling up. Chemical clastogens, which are toxic compounds found in some fast foods, can cause DNA damage and genomic instability. These include acridine yellow, benzene, ethylene oxide, arsenic, phosphine, actinomycin D, methotrexate, and methyl acrylate (Goel et al., 2023). Chemical clastogens cause harm by compromising the integrity of the genome, which is the entirety of an organism's genetic material that is encoded in DNA. These chemicals can cause chromosomal rearrangements, point mutations, DNA adducts, single and double-strand breaks, and other DNA lesions (Singh et al., 2024).

As humans age, our ability to detect damage and repair nuclear and mitochondrial DNA declines, resulting in genomic instability, a propensity to exhibit mutations, and the buildup of ectopic DNA in the cytosol which If left unsolved indefinitely, triggers apoptotic or cellular senescence-related pathways (Moskalev et al., 2013; López-Gil, et al., 2023; López-Otín et al., 2023). Therefore, the probability of cumulative genetic instability increases with cell age. This cumulative DNA damage is directly linked to age-related illnesses like neurological diseases and carcinogenesis (Kryston et al., 2011). Finding ways to improve DNA stability could therefore help lower the prevalence of Alzheimer's and cancer. One method that has been proposed is dietary restriction (Michan, 2014). A higher rate of DNA repair and a lower rate of DNA damage have been linked to eating fruits and vegetables (Slyskova et al., 2014).

2.2. Telomere attrition (genetic alteration)

Since the natural endpoints of linear chromosomes may be identified as double-strand breaks in DNA, they are poisonous to mammalian cells and cause genomic instability and harmful chromosomal rearrangement (Lazzerini-Denchi and Sfeir, 2016; Zhu et al., 2019).

Telomeres are dynamic chromosome-end complexes that are found at the end of linear eukaryotic chromosomes. They are made up of tandem repetitive DNA sequences and related protective proteins, and they are essential for preserving chromosome integrity and genomic stability, which in turn affects cell fate and aging (Tenchov et al., 2024). This is accomplished by structural protection mechanisms that guard against DNA loss at the ends during cell division and prevent chromosome end fusion, which determines cellular replicative potential (Franulic et al., 2024). Accordingly, telomere dysfunction and genomic instability seem to be crucial factors in cellular aging (Pusceddu et al., 2015; Xie et al., 2015). Since telomere length (TL) varies by species and is heritable (Chiang et al., 2010), its value at any one time is determined by genetic traits and the equilibrium between "shortening" and "elongation" signals (Honig et al., 2015). Numerous processes, including nuclease activation, oxidative damage, DNA replication, transcriptional stress, and repetitive cell division, can produce shortening signals (Blackburn et al., 2015). Alternative lengthening of telomeres (ALT), which depends on recombination-mediated telomere elongation and can be brought on by telomere-specific DNA damage, can be activated by elongation signals (Hu et al., 2016). Telomerase is an RNA-protein complex that uses integrated template-containing telomerase RNA (TER) and telomerase reverse transcriptase (TERT) to stretch telomeric DNA at the 3′ ends of chromosomes (Jiang et al., 2018). While telomerase is typically not activated in somatic cells, it is activated in embryonic cell lines and maintains TL constant; in adult stem cells, it has limited activity and only partially compensates for telomere shortening (TS). Therefore, shortening occurs more quickly than elongation during somatic cellular and organismal aging (Mensà et al., 2019) (Fig. 2).

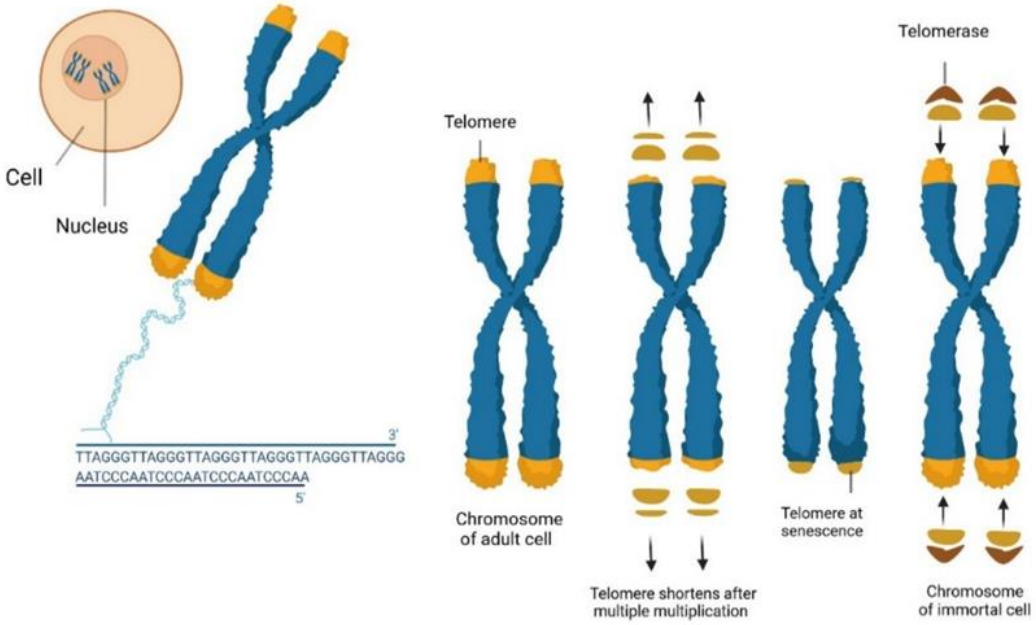

Fig. 2. Telomere shortening during aging

Mammalian telomeres are made up of lengthy TTAGGG repeat sequences that terminate in single-stranded G-rich 30 overhangs, or G-overhangs. These overhangs can range in size from 5 kb in human cells to 100 kb in mice, and they are linked to a protein complex called shelterin (Zhu et al., 2019). Six proteins make up the shelterin complex: repressor/activator protein (RAP1), protection of telomeres protein (POT1), TRF1-interacting nuclear protein 2 (TIN2), telomeric repeat binding factor 1 (TRF1), TRF2, and TIN2- and POT1-interacting protein (TPP1) (Lazzerini-Denchi and Sfeir, 2016; De Lange, 2018). By recruiting shelterin, changing their structure, and compacting telomere chromatin, the shelterin complex prevents damage signals at telomere ends known as the DNA damage response (DDR) from identifying chromosome ends as double-strand DNA damage. It also makes telomerase, a specialized DNA polymerase essential for highly replicative tissues, accessible. Telomere length preservation is the foundation of these defense mechanisms. However, the "end-replication problem" and telomere end processing cause telomeres to gradually shrink during cell division (Wu et al., 2012). Conversely, the CST complex protein (CTC1–STN1–TEN1) inhibits telomere over-elongation (Zhu et al., 2019; Gao et al., 2022) Although telomerase overexpression helps prevent aging, it also increases the risk of tumor development (Pereira and Ferreira, 2013).

2.3. Epigenetic alterations (DNA methylation)

The term "epigenetic alteration" describes modifications to gene expression that are accomplished without changing the base-pair structure of the DNA. Studies on genome-wide methylation have proposed that DNA methylation can predict human age (Bocklandt et al., 2011; Koch and Wagner, 2011; Hannum et al., 2013). A study that looked at the relationship between DNA methylation age and chronological age in older adults found that methylation status was associated with a higher risk of death, even when other known risk factors like smoking, diabetes, hypertension, and chronological age alone were not taken into account (Marioni et al., 2015). An additional investigation revealed that obesity was linked to elevated liver methylation (and accelerated aging), which may raise the risk of liver illness or cancer (Horvath et al., 2014).

Toxins and chemicals found in the environment, such as mercury, aluminum, dioxin, pesticides, asbestos, trichloroethylene, and many more, can cause oxidative stress and disrupt methyl group transfers, which leads to abnormal expression of DNA. The explanation for these expressions is believed to be epigenetic drifts, which are caused by minute variations or flaws in information expression that arise from cell divisions brought on by exposure to environmental substances. Thus, harmful substances can change epigenetic expressions, resulting in immunological dysregulation and the emergence of autoimmunity (Kharrazian, 2024).

2.4. Loss of proteostasis

In order to maintain the homeostasis of the proteome and the synthesis and turnover of human proteins, a group of cellular control mechanisms known as proteostasis work during protein synthesis (Eisenstein, 2014; Kaushik and Cuervo, 2015; López-Otín et al., 2023). One of its roles is to prevent damaged and malfunctioning polypeptides from misfolding and aggregating, which could endanger the cell's viability. It is made up of a network of three primary mechanisms: autophagy, proteasomal degradation, and chaperone-mediated folding.

2.4.1. Molecular chaperones

The tiny proteins known as molecular chaperones help native polypeptide chains fold into useful protein formats. Among these chaperones, the heat-shock family (HSF) of proteins is the most significant. As their name suggests, cellular stress, especially heat shock, increases the transcription of these chaperones (Chatterjee et al., 2018). The damage-associated molecular proteins (DAMPs), of which the heat-shock proteins are a component, are intimately linked to aging and the risk of cancer (Huang et al., 2015).

2.4.2. Proteolytic systems

In eukaryotic cells, proteasome is one of the main mechanisms for degradation. It is essential for maintaining the quality of proteins and other essential cellular functions, and it ends the existence of thousands of short-lived, damaged, misfolded, or otherwise obsolete proteins (Hoeller and Dikic, 2016). Proteasome activation is an evolutionarily

conserved process that delays aging in vivo and in vitro in a range of laboratory organisms (Chondrogianni et al., 2014). There are several diverse substances that can activate proteasomes, including pollen, spices, algal extract, dietary fatty acids, and several synthetic substances (Chondrogianni et al., 2014).

2.4.3. Autophagy

Your body uses autophagy as a cellular recycling mechanism. The cells use the lysosome-mediated breakdown of cytosolic components to eliminate intracellular pathogens, damaged organelles, and misfolded proteins (Yamamoto and Matsui, 2024). Mammals exhibit three primary forms of autophagy (Fig. 3): In macroautophagy, a double-membrane structure known as the phagophore or limiting membrane is formed. This structure sequesters parts of the cytoplasm, including whole proteins and organelles, and seals to create an autophagosome or double-membrane vesicle. The autophagosome is formed by more than 30 gene products, also referred to as autophagy-related or Atg proteins.

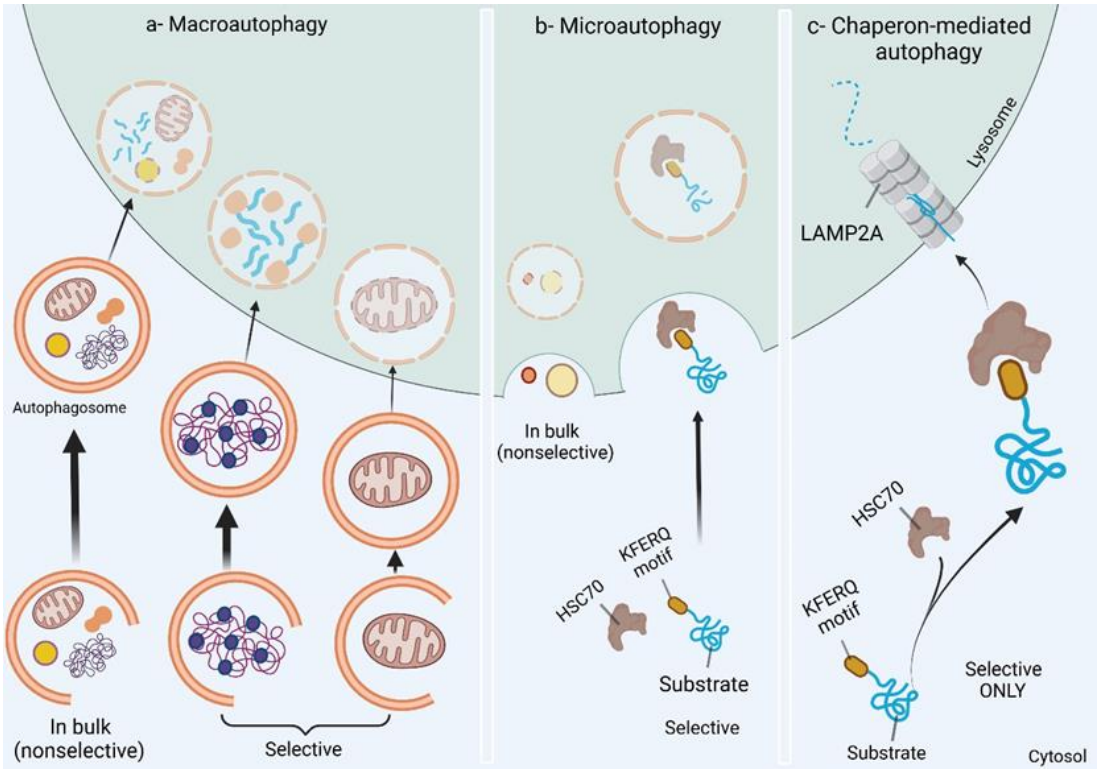

Fig. 3. Types of autophagy

When the autophagosome fuses with lysosomes, it gets the hydrolytic enzymes required to break down its cargo (He and Klionsky, 2009; Parzych and Klionsky, 2014; Yamamoto and Matsui, 2024). Similar to macroautophagy, microautophagy entails the nonspecific engulfment of cytoplasm, but by directly invaginating the lysosomal membrane to create intralysosomal vesicles that "pinch off" into the lumen and are broken down by lysosomal hydrolases there (Yamamoto and Matsui, 2024). In contrast to microautophagy and macroautophagy, which may both engulf bulk cytoplasm nonspecifically, the third form is called chaperone-mediated autophagy (CMA), which is extremely selective and shared by all CMA substrates, particularly the KFERQ motif (Parzych and Klionsky, 2014; Kacal et al., 2021). Cytosolic chaperones work to unfold target proteins with the KFERQ consensus motif, which are then translocated straight across the lysosomal membrane and broken down in the lumen (Orenstein and Cuervo, 2010; Parzych and Klionsky, 2014). The substrate attaches itself to lysosomal-associated membrane protein 2A (LAMP2A), one of the main protein constituents of the lysosomal membrane, and monomers of the CMA substrate receptor at the lysosomal membrane (Parzych and Klionsky, 2014; Kacal et al., 2021). Failure of any one of these three components of proteostasis might result in proteotoxic consequences and protein aggregation (López-Otín et al., 2013, 2023; Kaushik and Cuervo, 2015). Misfolded protein accumulation and aggregation are the main causes of several of the most prevalent age-related illnesses in people (Xie et al., 2023). In addition to non-neurodegenerative conditions like cataracts, these mostly comprise neurodegenerative conditions like Parkinson's and Alzheimer's illnesses. In old age and associated conditions, all of these illnesses are characterized by the regular presence of detergent-insoluble protein aggregates and inclusions (Labbadia and Morimoto, 2015).

2.5.Cellular senescence

Senescence, derived from the Latin word "senex," which means "growing old," is an irreversible type of long-term cell cycle stoppage brought on by significant extracellular or intracellular stress or damage (Noren Hooten and Evans, 2017; Dodig, et al., 2019). Cellular senescence, which frequently occurs in reaction to stress or damage, is a state where cells stop dividing but continue to function metabolically. According to the organism, it is characterized as proliferative arrest, which lowers the number of cells. Additionally, the ability for tissue regeneration will decline when stem cell senescence takes place, which accelerates aging (Zhu et al., 2019). Telomere disruption, oxidative stress, and oncogenic stress are some of the events that trigger cellular senescence. When senescent cells build up, they can cause increased inflammation, tissue dysfunction, and a decrease in the body's ability to regenerate (Chaib et

al., 2022). On the other hand, this process can be a part of physiological processes like bone growth during early puberty (Liu and Wan, 2019), or helpful as a defense mechanism against cancer (Franulic et al., 2024). However, senescent cells are metabolically and functionally active as changes take place, such as altered protein breakdown pathways, increased mitochondrial metabolism, and energy production (Salama et al., 2014; Dodig et al.,2019). Senescent cell arrest serves to stop injured cells from proliferating (i.e., from causing damage to be passed on to the next generation of cells), to get rid of accumulated toxic substances, and to stop possible malignant transformation (Coppé et al., 2010; Faragher et al., 2017; Yanagi et al., 2017; Dodig et al.,2019).

In vitro, cigarette smoke extract (CSE) can slow down mesenchymal stem cell osteogenic development and cause cellular aging (Aspera-Werz et al., 2018). Tobacco toxins may therefore be a major factor in smoking-related osteoporosis (SROP) by causing bone marrow mesenchymal stem cells (BMSCs) to age (Xiang et al., 2024). Mitochondrial failure is intimately associated with cellular senescence (Miwa et al., 2022). The overproduction of ROS caused by mitochondrial malfunction sets off an oxidative stress response that can start a DNA damage response (DDR) and ultimately result in cellular senescence. A quality control process called mitophagy plays a crucial role in preserving mitochondrial homeostasis by specifically removing damaged mitochondria and enabling the restoration of cellular structures and functions (Sun et al., 2015). Research has indicated that the accumulation of intracellular ROS caused by CSE results in oxidative stress, mitochondrial malfunction, and the inhibition of mitophagy (Xiang et al., 2024).

Senescence can be divided into two primary groups based on the kinetics of cell senescence (Fig. 4): acute (transient) senescence and chronic (permanent) senescence (van Deursen, 2014). As a natural biological process, acute senescence benefits tissue because it may be a component of a planned mechanism that controls fibrosis during tissue repair (Jun and Lau, 2010; Dodig et al., 2019). Senescence-associated secretory phenotype (SASP) factors are activated, which in turn triggers immunological clearance, which eliminates acute senescent cells. Conversely, chronic senescence has negative impacts on cells and tissues due to the great resistance of senescent cells to immune clearance and the significant SASP variability involved in chronic (Dodig et al., 2019).

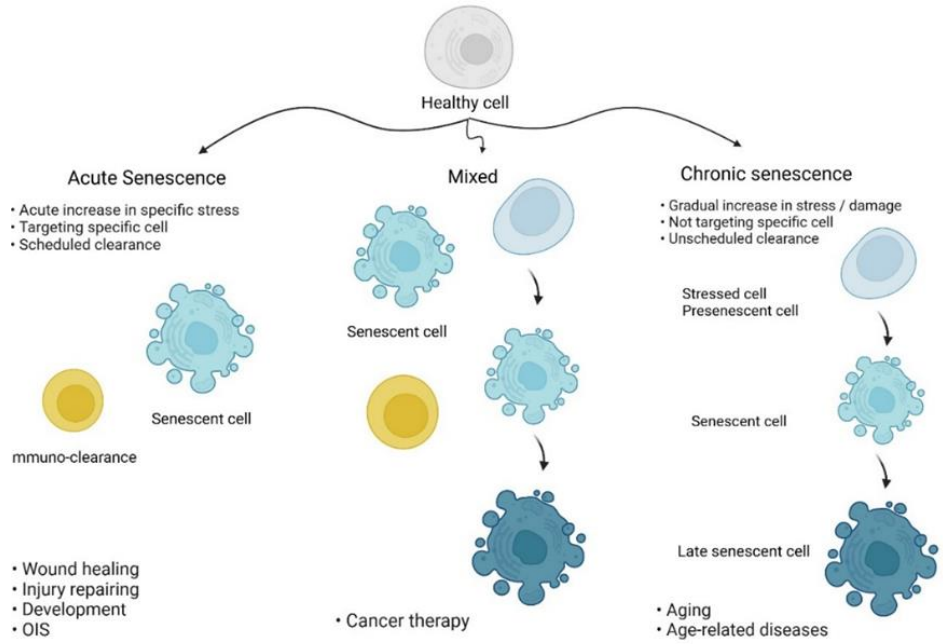

Fig. 4. Cellular senescence

2.6. Chronic inflammation (inflammaging)

In contrast to acute (transient) inflammation, which is resolved when the causing chemicals are eliminated and the damaged tissue is repaired, chronic inflammation lasts for a very long time. When there is persistent inflammation, macrophages, and lymphocytes invade the afflicted tissues. Furthermore, there may be fibrous and necrotic tissue damage (Freund et al., 2010; Goldberg and Dixit, 2015; Dodig, et al., 2019). It has been reported that aging causes persistent, low-grade, and unresolved condition of inflammation. This disorder is caused by tissue damage accumulation, senescent cells' pro-inflammatory secretome, and adaptive immune system failure, which results in impaired immune-surveillance and tolerance loss (Fulop et al., 2023; López-Otín et al., 2023; Li and Ma, 2024). Normal, healthy aging is characterized by significantly higher serum concentrations of pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, IL-22, IL-23, IFN-γ, TNF-α) than in younger people (Minciullo et al., 2016; Ventura et al., 2017; Rea et al., 2018). At the same time, older adults have higher levels of anti-inflammatory cytokines (transforming growth factor beta 1 (TGF-β1), IL-1 receptor antagonist (IL-1Ra), IL-4, IL-10, and IL-37) than younger adults. Anti-inflammatory cytokines work to protect tissues by counteracting pro-inflammatory cytokine activity and lowering chronic inflammation. Pro-inflammatory and anti-inflammatory mediators have been found to work in balance during healthy aging. Conversely, their imbalance causes the body to age and gives rise to several age-related medical disorders (Dodig et al., 2019).

Lastly, we may think of inflammation as the outcome of several disorders that originate from each of the previous hallmarks. Therefore, chronic inflammation will result from any chemicals and environmental pollutants that cause cellular senescence, dysbiosis, loss of proteostasis, telomere attrition, genomic instability, and epigenetic modifications such as mycotoxins, some heavy metals, cigarette smoke extract, mercury, and chemical clastogens.

2.7.Dysbiosis

Unbalanced bacterial composition, altered bacterial metabolic processes, or altered bacterial distribution in the gut are all examples of dysbiosis. Dysbiosis comes in three forms: loss of total bacterial diversity, overgrowth of potentially harmful bacteria, and loss of helpful bacteria.

A new characteristic of aging is dysbiosis, which is characterized by abnormalities in the exchange of information between the host and the microbiota, which is necessary for several physiologi-cal functions (López-Otín et al., 2023). Research on both humans and animals has shown that as people age, their microbiomes become less diverse and stable (Fig. 5) (Buford, 2017) and different patterns of microbial composition are linked to different health and longevity outcomes (Badal et al., 2020; López-Otín et al., 2023). Recent research evaluating the administration of Lactobacillus plantarum (LP), a significant probiotic agent, in young and old mice revealed positive effects on muscle function and glycogen levels, as well as a reduction in age-related bone loss and bone quality (Table 1). This was linked to a shift in the composition of the microbiota, which decreased the buildup of harmful organisms as people aged (Lee et al., 2021). Significant antioxidant capacity has been demonstrated by LP in the D-galactose-induced aging mouse model. LP gavage can lower blood urea, muscle glycogen levels, malondialdehyde, alanine aminotransferase, aspartate aminotransferase, and antioxidant activities while also improving mice's general endurance (Gupta et al., 2024). Diet, surroundings, and improper use of antibiotics and xenobiotics can change the gut microbiota's natural makeup and cause microbial dysbiosis-related health problems like diabetes, atherosclerosis, cirrhosis, intestinal cancer, arthritis, and hypertension (Li et al., 2017; Gupta et al., 2022, 2024). Intestinal microbial dysbiosis is also caused by some toxic substances like certain mycotoxins. It was discovered that it was linked to elevated inflammatory markers in the colon following aflatoxin B1 (AFB1) exposure (Zhang et al., 2024).

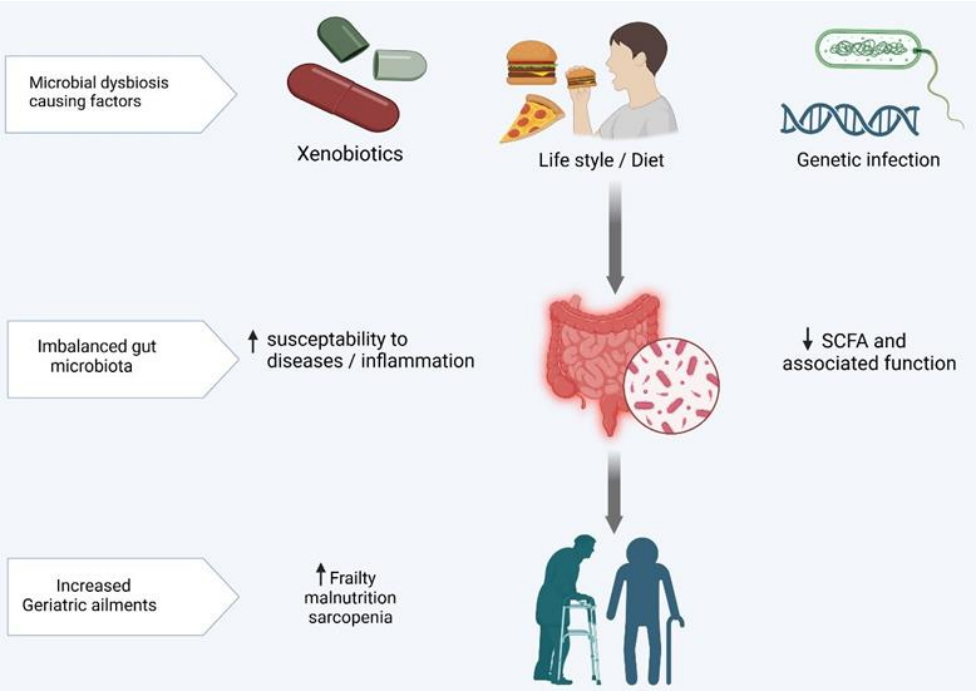

Fig. 5. Gut dysbiosis

Table 1. Recent findings on the effect of various strains of *L. plantarum* on aging models

L. plantarum strains	Model organism	Key finding	References
L. plantarum ZS62	Mice	Prevents morphological changes in hepatocytes via anti-inflammation and anti-oxidant pathways.	(Gan et al., 2021)
L. plantarum NJAU-01	Mice	Prevents galactose-induced aging	(Ge et al., 2021)
L. plantarum JBC5	Roundworm (Caenorhabditis elegans)	Promotes healthy aging, gut integrity, and overall lifespan	(Kumar et al., 2022)
L. plantarum KSFY01	Mice	Activation of the Nrf2 improved the athletic ability of mice.	(Chen et al., 2022)
L. plantarum JBMI F5	Human foreskin fibroblast cell line, Mice	Anti-photo aging (skin aging due to Ultraviolet radiation). Prevents UVB induced wrinkles.	(Kim et al., 2019)
L. plantarum69–2	Mice	Increased SCFA levels alleviate signs of aging via the liver-gut axis.	(Wang et al., 2021)

3. CONCLUSIONS

In order to understand how physiological aging occurs, we shall talk about the signs of aging and its causes. Most environmental pollutants and chemicals such as mycotoxins, heavy metals, tobacco, mercury, and chemical clastogens accelerate the aging process. Therefore, studying the biological effects of aging is crucial to developing effective and safe intervention strategies to enhance health and lengthen people's lifespans. Signs of aging may be genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, cellular senescence, chronic inflammation, and /or dysbiosis.

Abbreviations: TL, telomere length; ALT, Alternative lengthening of telomeres; TER, template-containing telomerase RNA; TERT, telomerase reverse transcriptase; TS, telomere shortening; RAP1, repressor/activator protein; POT1, protection of telomeres protein; TIN2, TRF1-interacting nuclear protein 2; TRF1, telomeric repeat binding factor 1; TPP1, TRF2, TIN2- and POT1-interacting protein; DDR, DNA damage response; CST complex protein, CTC1–STN1–TEN1; HSF, heat-shock family; DAMPs, damage-associated molecular proteins; Atg proteins, autophagy-related protein; CMA, chaperone-mediated autophagy; LAMP2A, lysosomal-associated membrane protein 2A; CSE, cigarette smoke extract; SROP, smoking-related osteoporosis; BMSCs, bone marrow mesenchymal stem cells; SASP, Senescence-associated secretory phenotype; IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor alpha; TGF-β1, transforming growth factor beta 1; IL-1Ra, IL-1 receptor antagonist; LP, Lactobacillus plantarum.

Author Contributions:

All authors made substantial contributions to the work described, whether in the areas of development, planning, and implementation, data collection, analysis, and comprehension, or all of these; they also wrote, edited, or critically reviewed the article; they gave their final approval for the version to be published; they chose the journal to which the article was submitted; and they agreed to take responsibility for every part of the work.

Data Availability Statement:

Not applicable

Conflicts of Interest:

No conflicts of interest are disclosed by the writers.

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