Open Access

OBM Geriatrics

LIDSEN Publishing Inc.

Short Review

Age-Related Pathologies and Life Span

Giuseppe Cocco [1,*], Stefano Pandolfi [2]

1. FMH Internal Medicine special Cardiology, Rheumatology, Weiermattstrasse 41, CH-4153 Reinach Switzerland; E-Mail: praxis@cocco.ch
2. FMH Rheumatology and General Internal Medicine, Salina Medizin, Roberstenstrasse 31, CH-4310 Rheinfelden Switzerland; E-Mail: Stefano.Pandolfi@parkresort.ch

* **Correspondence:** Giuseppe Cocco; E-Mail: praxis@cocco.ch

Academic Editor: Calogero Caruso

OBM Geriatrics
2023, volume 7, issue 4
doi:10.21926/obm.geriatr.2304253

Received: July 27, 2023
Accepted: September 27, 2023
Published: October 11, 2023

Abstract

Both from a healthcare and a socioeconomic perspective, research on senescence is increasingly essential. Indeed, in industrialized countries, the increased human longevity confronts medicine with many old patients with age-related pathologies. The paper reviews the biological theories on aging, the impact of reactive oxygen species, telomers, epigenetics, and genetics (e.g., gerontogenes) on-age-related pathologies. Also, the paper reviews available and under research therapeutic approaches (e.g., senolytics) aimed to prolong life span and reduce the morbidity related to old age.

Keywords

Longevity; theories on aging; epigenetics; genetics

1. Introduction

In many countries, life expectancy started to increase around 1840 at a pace of almost 2.5 years per decade, which has continued until the present [1]. Contrary to classical evolutionary theories of

aging and contrary to the predictions of many experts, the frontier of survival is advancing to higher ages [1]. If the progress in life expectancy continues, most children born this millennium will celebrate their 100th birthday [1]. Furthermore, individual life spans are becoming more equal, reducing inequalities, with octogenarians and nonagenarians accounting for most deaths in countries with the highest life expectancy [1]. However, aging is the leading risk factor for multiple chronic severe diseases and disabilities and is a significant driver of morbidity, mortality, and health costs [2].

2. Biodemography

Recent biodemographic studies of aging and longevity call into question conventional aging theories and open up novel research directions. A top scientific theme is the question of how much human life span can be extended with a good quality of life [3]. It has been found that the exponential increase of the mortality risk with age (the Gompertz law) continues even at extremely old ages in mice, rats, and humans, thus challenging traditional views about old-age mortality deceleration, mortality leveling-off and late-life mortality plateaus [3]. Another significant recent development is the discovery of long-term memory for early-life experiences in longevity determination. Siblings born to young mothers have significantly higher chances to live up to 100 years, and even the place and season of birth matter for human longevity [3]. Beneficial longevity effects of young maternal age are observed only when children of the same parents are compared. In contrast, the maternal age effect often could not be detected in across-families' studies, presumably being masked by between-family variation [3]. It was also found that the male gender of centenarians has a significant positive on the survival of adult male biological relatives (brothers and fathers) but not of female relatives [3]. Finally, large gender differences are found in longevity determinants for males and females, suggesting a higher importance of occupation history for male centenarians and a higher importance of home environment history for female centenarians [3]. These findings call for an explanation.

3. Longevity Medicine

Longevity medicine is a fast-emerging field, which encompasses the likewise rapidly evolving areas of biogerontology, geroscience, and precision, preventive, and functional medicine [4]. Longevity medicine uses modern advances in artificial intelligence and machine learning, biomarker research, and drug development with many tools for early diagnostics and prevention of communicable and non-communicable diseases [4].

At present longevity, medicine remains largely unknown to the global medical community, mainly due to a complete absence of structured, pedagogically conceived educational resources tailored to specific audiences, primarily consisting of physicians, biotechnologists, and public health professionals [4].

4. Cellular Senescence

Senescent cells were discovered in 1961 and appear at pathogenic sites of many major diseases [2]. Cellular senescence contributes to age-related dysfunction and multiple disorders throughout the lifespan. Senescent cells frequently are metabolically shifted from fatty acid utilization toward

glycolysis, resulting in reactive oxygen species (ROS) generation, lipid accumulation, lipotoxicity, and dedifferentiation into fat cell-like but insulin-resistant mesenchymal adipocyte-like default cells. Senescent cells are resistant to death [2].

Senescence is a cell fate, like differentiation, proliferation, apoptosis, and necrosis. External and internal signals can contribute to driving a cell into senescence.[2].

Accumulation of senescent cells can cause local and systemic inflammation, tissue destruction, immune system inhibition, and stem and progenitor cell dysfunction due to their senescence-associated secretory phenotype (SASP). Generally, 30-70% of senescent cells develop a SASP comprising proinflammatory cytokines, chemokines, proteases, procoagulant factors, stem/progenitor cell poisons, growth factors, bioactive lipids (prostanoids, saturated ceramides, bradykinins), miRNA's, non-coding but biologically active nucleotides, and microvescicles including exosomes. The SASP depends on the type of cell that became senescent, how senescence was induced, and its milieu. Due to their SASP, only a few senescent cells can cause considerable dysfunction. Senescent cells are usually cleared by the immune system [2]. However, above a threshold burden, senescent cells interfere with the immune system and its ability to remove them. Several data support the hypothesis that there is a threshold above which senescent cell burden due to the spread of senescence becomes self-amplifying, which presages increased risk for senescence and age-related phenotypes and diseases, perhaps contributing to age-related multimorbidity [2].

5. Biological Theories of Aging

There are two main categories: a) programmed and b) damage (or error) theories. They interact with each other in a complex way, and none of the theories nor their combination is entirely satisfactory for explaining senescence and longevity [5].

The three **programmed** theories hold that aging follows a biological timetable, perhaps a continuation of the one that regulates childhood growth and development. This regulation would depend on changes in gene expression that affect the systems responsible for maintenance, repair, and defense responses [5].

a) The *longevity* theory holds that aging would result from a sequential switching on and off of specific genes, with senescence being defined as the time when age-associated deficits are manifested [5].

b) The *endocrine* theory holds that biological clocks act through hormones to control the pace of aging. Recent studies confirm that aging is hormonally regulated and that the evolutionarily conserved insulin/IGF-1 signaling pathway plays a key role in the hormonal regulation of aging [5].

c) The *immunological* theory holds that the immune system is programmed to decline over time, which leads to an increased vulnerability to infectious disease and, thus, aging and death. As one ages, antibodies lose their effectiveness, and the body cannot combat new diseases effectively [5]. The consequences are cellular stress and, eventually, death. Dysregulated immune response has been linked to cardiovascular pathologies, inflammation, Alzheimer's disease, and cancer.

Indeed, new data show that in mice, immunosenescence (aging of the immune system) contributes to morbidity and mortality and has a causal role in driving systemic aging [6]. Furthermore, some studies in patients [7-12] have reported that aging induces detrimental epigenetic changes and reduces new immune memory: in older adults, immune cells show global

DNA hypermethylation and a more closed chromatin pattern at the T-lymphocyte factor 1. This reduces the memory for the formation of immunity and alters the function of the IL-7 receptor that is required for the survival of memory cells. These changes might explain why the elderly have increased susceptibility to infections, decreased response to immunization, and increased risk of cancer and autoimmune diseases.

There are may **damage** (or **error**) theories. They hold that the cause of aging is neither an adaptation nor a genetically programmed process. Environmental assaults would cause aging to live organisms that induce cumulative damage at various levels [5].

a) The *wear and tear* theory was first introduced in 1882 by the German biologist Weisman and holds that cells and tissues have vital parts that wear out, resulting in aging and death [5].

b) The *rate of living* theory holds that the greater an organism's rate of oxygen basal metabolism, the shorter its lifespan. A modified version emphasizes the hard-wired antagonism of growth and stress resistance [5].

c) The *cross-linking* theory was proposed in 1942 by Bjorksten and holds that aging results from an accumulation of cross-linked proteins that damages cells and tissues, which slows down bodily processes [5]. Several variations of this theory suggest that aging would start with the earlier reproductive phase of life and that the energetic resources invested in reproduction or longevity would determine the lifespan of living organisms [6].

d) The *free radical* theory was first introduced in 1954 by Gerschman, but it was developed in 1956 by Harman [7, 8]. This theory holds that age-related processes arise from the accumulation of toxic molecules [9, 10].

The energy released by nutrients is converted by oxidative phosphorylation into adenosine triphosphate, the principal source of power of cells. Oxygen is the final electron acceptor of this process, but up to 3% of the oxygen is reduced insufficiently, with consequent production of ROS [9, 11]. ROS are produced primarily in the cellular mitochondria, but they are also generated from other cellular processes in which oxidation takes place and also from exogenous sources, e.g., ultraviolet radiation [6]. Cytochrome p450, NADPH oxidase (Nox), and uncoupled endothelial nitric oxide (NO) synthase (eNOS) are identified as enzymatic sources of ROS [9, 11]. In youthful age the level of intracellular ROS is downregulated by enzymatic and non-enzymatic antioxidants. In aging the mitochondrial and extra-mitochondrial production of ROS increases with consequential damage of the mitochondrial DNA. ROS accumulate in the cells, and Nox generates superoxide anions, which further promote eNOS uncoupling, blunted NO bioavailability, and increased levels of ROS.

Furthermore, in aging, the production of antioxidants (catalase, dismutase, glutathione, and superoxide dismutase) decreases, and the cellular repairing mechanisms against oxidants become dysfunctional. The age-related increased ROS-production triggers the activation of the nuclear factor k-light-chain enhancer of activated B cells (NF-κB), essential in the inflammatory processes that characterize many clinical arteriosclerotic pathologies. In turn, NF-κB upregulates the expression of adhesion molecules, cytokines, and proinflammatory genes [12]. The high levels of cellular ROS generate toxic molecules (e.g., peroxynitrite), which disrupt mitochondrial activity and derange lipoprotein oxidation.

In summary, the free radical theory implies that high levels of ROS are the crucial force of aging and determine longevity. Classically, inflammation is triggered by pathogen recognition and by tissue damage. However, it is now accepted that aging and other pathologies also induce a sterile, low-grade, and long-lasting inflammation, called *inflammaging*, that is characterized by high levels

of the pentameric short pentraxin C-reactive protein (CRP) (also called PTX_1), interleukin-6 (IL-6), NF-κB and the vascular cell adhesion molecule-1 [13-20]. In humans, CRP is a prototypic liver-derived acute protein [21]. Senescent cells show an abnormal secretory phenotype that is characterized by the release of chemokines, cytokines, growth factors, and proteases [22-23]. Several studies in patients have shown that, in a paracrine manner, the released inflammatory molecules contribute to immunosenescence and inflammaging with related neurologic and cardiovascular pathologies. Genetic polymorphisms are associated with increased CRP levels, and increased circulating CRP levels are linked to an increased risk for coronary artery disease [6]. However, the widely observed associations between CRP and cardiovascular pathologies are more likely to be explained by confounding in observational studies and by treatments in clinical trials, and CRP should not be used to assess lifespan longevity because it is unlikely to be a cause of cardiovascular pathologies [21-23]. Indeed, mendelian randomization studies demonstrated that there is no causality between CRP concentration and cardiovascular pathologies [24, 25]. Nonetheless, increased levels of CRP, IL-6, and other inflammatory biomarkers are common hallmarks of atherosclerosis in geriatric patients and correlate with cardiovascular pathologies [18-21]. In a study in patients with previous myocardial infarction who presented increased systemic inflammation the therapy with canakinumab (an anti-IL-1β antibody) they significantly reduced the occurrence of adverse cardiovascular events, supporting the hypothesis that inflammation plays a role in lowering longevity [18-20].

e) The *telomere deterioration* theory holds that telomeres shortening should cause age-related senescence and reduced lifespan.

Telomeres are dynamic chromosome-end structures that serve as guardians of genome stability, being biological clocks that stabilize cell replication by repairing and protecting the genome from nucleolytic degradation and interchromosomal fusion. In human cells with an active telomerase complex, telomeres consist of TTAGGG repeats, added to the ends of the chromosomes by the catalytic subunit tert and the RNA template subunit terc [6]. While the enzyme telomerase preserves the length of telomere by synthesizing new telomeric DNAs to compensate for telomeric loss during each cell division, studies in cultured human cells have proven that telomeres shorten with every cell cycle until reaching a critical length at which point the cell enters senescence, cannot undergo dividing, and dies [6, 26-30].

The telomere deterioration theory is based on the consistent findings of a negative correlation between telomere length and replicative potential of cultured cells, as well as a decreasing telomere length in several different tissues in humans with age. Telomere shortening to a critical length can trigger aging, and shorter life spans in mice and humans by a mechanism that involves the induction of a persistent DNA damage response at chromosome ends and loss of cellular viability.

Most data support the notion that critical telomere shortening and the consequent onset of telomeric DNA damage and cellular senescence are some of the significant determinants of aging and longevity in higher mammals [26-28]. A study [30] found that a subset of human adults may reach the telomeric brink within the current life expectancy and more so for a 100-year life expectancy. Another study [31] in a wide variety of species (birds and mammals) with very different life spans and body sizes found that the telomere shortening rate, but not the initial telomere length alone, is a powerful predictor of species life span.

Of note, there are sex differences in telomeres (in humans, men have shorter lifespans and greater telomere shortening), which might influence different lifespans [32].

However, although it is well established that telomere shortening has an essential role in the i*n vitro* aging of somatic cells, there is so far no conclusive evidence of an in vivo involvement of telomere erosion in aging, and two large meta-analyses and genetic analyses found that alleles associated with short telomeres are associated with cardiovascular pathologies but have primarily excluded the possibility that telomeres shortening is cause for cardiovascular pathologies [27, 28]. Also, it is unknown whether telomere length is a universal determinant of species longevity [31, 33]. In summary, while much remains to be resolved, telomere dynamics nevertheless provide a promising mechanistic basis for studying aging and lifespan hypotheses across disciplines.

f) The *DNA instability* theory holds on the fact that ROS and external sources (such as ionizing radiation) favor the occurrence of DNA damage [5]. At young age, several DNA repair mechanisms generally ensure the removal of the different types of DNA damage before they are converted to mutations but in aging irreparable double DNA breaks occur in telomeres and cause cellular senescence and death, even if telomeres are not critically short [34-36]. The Rothmund-Thomson and Werner syndromes are characterized by premature aging caused by mutations in DNA repair protein-encoding genes and are cited to support the relevance of the DNA instability theory [6].

The damage theories also recognize that several genes play a significant role in inducing age-related changes [6]. While none of the proposed ideas, nor their combination is entirely satisfactory for explaining senescence and longevity [5], the free radical (ROS), telomere shortening, and DNA instability theories play a crucial role in replicative senescence, which in turn is responsible for organismal aging.

6. Gene Expression and Gerontogenes

A large amount of data [2, 6, 37] has shown that in senescent cells, gene expression is impaired, the division rate slows down, and the sensitivity to intra- and extracellular stimuli is reduced. These age-related changes are the basis for many pathologies that are the most important cause of diseases and death in older adults [2, 6, 37]. *Evolutionary theories* of aging predict the existence of specific genes that provide selective advantage early in life with adverse effects on lifespan later in life (*antagonistic pleiotropy theory*) or longevity insurance genes (*disposable soma theory*). Indeed, the study of animal and human genetics is gradually identifying new genes (*gerontogenes*) that increase lifespan when overexpressed or mutated: gerontogenes. Furthermore, genetic and epigenetic mechanisms are being identified that positively affect longevity [6, 38-42].

Gerontogenes are classified as lifespan regulators, mediators, effectors, housekeeping genes, genes involved in mitochondrial function, and genes regulating cellular senescence and apoptosis. Notably, genes specific to a given population are believed to play a more important role than those shared between different people. This occurs because gene-environment interactions are typical for a given population due to the variability of environmental and cultural contexts such as, among others, food habits and lifestyle [43].

Despite efforts and new technologies, only two genes, APOE and FOXO3A, have been shown to be associated with longevity in nearly all studies [43]. APOE was identified almost 30 years ago as one of the most vital and most reproducible genetic risk factors for late-onset Alzheimer's disease [44]. Longevity-associated alleles of *FOXO3* reduce age-related mortality are (involved in the protection of cardiovascular diseases) and the mechanism is currently of great clinical interest [45].

Recent intriguing empirical observations also suggest that inherited epigenetic effects could influence lifespan/longevity in various organisms and *epigenetics* has come to the fore as a discipline central to biogerontology [4, 5]. Aging-associated epigenetic changes include DNA methylation, histone modification, chromatin remodeling, non-coding RNA (ncRNA) regulation, and RNA modification, all of which participate in the law of the aging process, and hence contribute to aging-related diseases; these changes are routinely linked with pathologies, including cardiovascular disease, cancer, and Alzheimer's disease [46-51]. Moreover, epigenetic clocks can correlate biological age with chronological age in many species, including humans [46-51]. Indeed, studies of chromatin changes found that in aging, epigenetics plays a vital role in longevity with two recurring themes: a) global upregulation of activating marks and downregulation of repressive marks, and b) gene-specific changes in chromatin states regulating expression of crucial longevity genes. These general themes are heavily influenced by environmental stimuli, nutrient signaling, and metabolic state [46-51].

Variations in *genotypes* are abundant, usually with little if any relevance on lifespan, but small-size variations (copy number variations, tandem repeats, insertions/deletions of single nucleotides, and single nucleotide polymorphism are considered active in determining longevity [4, 6, 43]. A study in engineered mice [52] found that genetic modifications of the *β-adrenergic system* affect their lifespan, and a clinical study [53] found that two common genetic variants of ADRB2 [rs1042718 (C/A) and rs1042719 (G/C)] suppress its translation and, in men, are predominantly associated with longevity.

7. Gerontones wit Effects on the Cardiovascular and Nervous System

The gene **JunD** is one of the three DNA-binding proteins of the activating protein-1, which in humans JunD is located in chromosome 9 [54]. Mice experiments [55] have proven that JunD regulates cellular growth and survival by modulating oxidative stress levels. Reduced JunD level throws off the balance between oxidants (e.g., NADPH oxidase) and scavengers' enzymes and favor ROS accumulation, with consequent mitochondrial and endothelial dysfunction. In JunD deleted mice, ROS levels are increased, and, despite normal appearance at birth, the mice develop premature signs of senescence, while JunD overexpression preserves endothelial function. In a mice experiment [56], the middle cerebral artery was transiently ligated: JunD knock-out mice suffered larger cerebral infarctions and had worse neurologic outcomes than normal mice; the addition of the IL-1β antibody canakinumab upon reperfusion rescued the harmful effect of JunD silencing, suggesting that the worse results in JunD-knock-out mice should be a consequence of increased inflammation, due to high IL-1β levels in cerebral tissues. Thus, experimental data show that aging reduces JunD expression. Experimental data were partially confirmed in patients [57] because it was found that monocytes of elderly persons show significantly less JunD expression than those of young subjects.

In humans, the gene *Klotho* is located in chromosome 13q13.1 [58]. Mice experiments [59-61] have shown that the Klotho gene reduces cardiovascular pathology by blunting the oxidative stress; Klotho deficient mice show lower vascular and systemic NO production, increased urinary expression of NO metabolites, and develop early aortic calcification, and restoring Klotho expression in Klotho depleted mice upregulates mitochondrial antioxidant enzyme activity, reduces cardiac remodeling and reverses vascular aging. Some experimental data have been confirmed in clinical

observational trials [62-64]: in patients with acute cardiac ischemia, the administration of the Klotho protein reduced the ischemia/reperfusion injury; also the Klotho expression was downregulated in the myocardium of patients with high cardiovascular risks, and the reduced expression paralleled systemic fibrosis, inflammation, and oxidative stress; lastly, the level of Klotho protein was increased in patients with cardiomyopathy and those with coronary artery disease.

The mammal target of rapamycin gene, uc001asd.3, position: hg19 chr1: 11, 166, 588-11, 322, 608 (*mTOR*) belongs to the phosphoinositide kinase-related family; in mammals exist two subunits of mTOR: mTOR1, that is involved in cellular growth and prolongs lifespan, and mTOR2, that plays a key role in cellular architecture [65-68]. Rapamycin (also called sirolimus) derives its name from Rapa nui, the word (in the language of inhabitants of the Easter Island) of a protein that was extracted from soil samples containing Streptomyces bacteria. Rapamycin has many effects and is a potent immunosuppressant that interacts with T lymphocytes and dendritic cells. Rapamycin is used to inhibit the mTOR gene. Mice experiments [66-68] have shown that mTOR plays a crucial role on the cardiovascular system. mTOR1 deleted mice show a high rate of embryonic lethality due to cardiovascular pathologies, evidencing that mTOR is essential in the cardiovascular system's embryonal development and postnatal function. Also, in adult mice specific cardiac deletion of mTOR1 with rapamycin enhances vasodilation. Lastly, long-term supplementation with rapamycin in old mice reduces age-related cardiac inflammation and arterial collagen degeneration, consequently reducing arterial resistance, hypertension, and systolic dysfunction. Some clinical trials have confirmed the validity of some experimental data [69, 70]. In renal transplanted patients, the inhibition of mTOR with rapamycin increased ROS signaling and thus decreased arterial resistance, blood pressure, and endothelial dysfunction. Unfortunately, long-term therapy with rapamycin is hampered by its adverse effects, such as hyperlipidemia, insulin resistance, and the occurrence of diabetes mellitus.

The *SHC1 gene* encodes the phosphorylated isomer of the adaptor protein *p66^{shc}* GATAD2A. When activated, p66^{shc} translocates from the cytosol to the mitochondria, mediates the release of cytochrome C into the cytoplasm, increases ROS production, and induces cell death by apoptosis [71-73]. Several mice experiments [74-76] have outlined that the p66^{shc} gene plays a crucial role in age-related changes in the cardiovascular and nervous systems. Indeed, mice lacking p66^{shc} show preserved endothelial NO bioavailability with reduced ROS production and are protected against endothelial dysfunction. Also, deletion of p66^{shc} increases the resistance to oxidative stress-induced apoptosis and decreases the production of intracellular oxidants, with a consequent 30% prolongation of their life span. Moreover, in diabetic mice hyperglycemia promotes phosphorylation of p66^{shc} with consequent reduction of NO bioavailability and increased ROS formation, and silencing the p66 gene decreases ROS production, restores endothelial relaxation, and delays apoptosis. Other experiments found that in p66^{shc} knock-out mice there is decreased accumulation of intimal foam cells in the arteries and oxidized low-density cholesterol, resulting in reduced oxidative stress is reduced consequently, these mice have a lower rate of atherogenesis. Moreover, in other mice experiment, the basilar arteries were transiently ligated: p66^{shc} knock-out mice had smaller ROS production and smaller cerebral strokes than normal mice.

In summary, many experimental studies indicate that the p66^{shc} gene should be crucial in atherosclerosis. Some clinical trials have confirmed experimental data [77-80]. In patients with acute cerebral stroke, p66^{shc} gene expression was highly increased, and the level correlated with short-term neurological outcomes. Also, the p66 mRNA concentration is significantly higher in

patients with acute cardiac ischemic events than in patients with stable coronary artery disease and healthy subjects. Lastly, in patients with chronic coronary artery disease, the p66 mRNA concentration is increased in circulating mononuclear cells. However, the results from a mice experiment [81] outline that the cardiovascular effect of the $p66^{shc}$ gene is not entirely elucidated because the transient ligation of the left anterior coronary artery induced larger myocardial infarctions in $p66^{shc}$ knock-out mice than in normal mice (the authors explain this effect by a blunted activation of protective pathways).

The silent information regulator 2 protein sirtuin (*SIRT)* gene with genomic sequence chr10: 69, 644, 427-69, 678, 147 belongs to the class III histone deacetylase family [82]. In mammals, there are 7 different SIRT genes with different concentrations in various organs. Many mice experiments [6, 83, 84] indicate that SIRT genes are crucial players in the nervous and cardiovascular systems. Some effects of SIRT1 (improved cardiac contraction, reduced blood pressure and cardiac remodeling, and decreased occurrence of stroke and myocardial infarction) are cardioprotective. In an experiment with ApoE-mice fed with high fat diet, the SIRT1 overexpression decreased ROS formation and blunted NF-κB activity in endothelial cells [85].

On the other hand, the effects of SIRT2 on the cardiac and nervous system may be either protective or deleterious [86-88]. In mice, the left anterior coronary artery was ligated: mice lacking SIRT1 and/or SIRT3 had less ischemic damage, reperfusion injury, and smaller myocardial infarcts than normal mice (protective effect) [86]. In another experiment [88], the aorta was constricted, and SIRT3 knock-out mice had more cardiac hypertrophy than normal mice (negative effect). Also, in mice, the transient occlusion of the middle cerebral artery induced larger cerebral infarctions and increased mortality in mice lacking SIRT5 than in normal mice, suggesting that SIRT5 should exert protective effects on the integrity of the brain barrier of the cerebral circulation [89]. However, in another mice experiment [90], SIRT3-deficient mice did not show a reduced coronary vulnerability and cardiac damage, but weight gain was accelerated, and the LDL-cholesterol metabolism was worse. Clinical studies genes confirmed that SIRT genes play a crucial role in the vascular system and that effects were either positive or negative. Circulating mononuclear blood cells collected from patients with cerebral stroke expressed more SIRT5 than those from control subjects, and the increased SIRT5 expression paralleled the size of the cerebral injury; furthermore, SIRT5 gene silencing in vivo resulted in reduced stroke size and improved neurological outcomes [91]. On the other hand, in peripheral CD14+ monocytes, the expression of the SIRT3 mRNA was lower in patients with ST-elevation myocardial infarct than in healthy controls, and the activity of plasma tissue factors was upregulated, with the formation of neutrophil extracellular traps and acceleration of the thrombotic process (harmful effects) [92]. In summary, many experimental and some clinical observational studies show that SIRT genes play a crucial role in regulating the function of the cardiovascular and nervous systems. Still, it is as yet unclear when the effect is positive or negative.

8. Therapy of Age-Related Pathologies

Many experimental studies in rodents and some observational studies in patients have outlined that inflammation and immunosenescence are two faces of the same coin and have proven the crucial impact of oxidative stress on aging and lifespan [12, 13, 15]. Many trials tested antioxidants in age-related pathologies without finding a positive effect [6].

In 2004 it was discovered that calorically restricted Ames dwarf mice with pituitary hormone deficiencies showed delayed senescent cell accumulation and had increased health- and lifespan [2]. Many research experiments tested the effects of reduced caloric apport in mice. Reducing caloric apport maintained NO bioavailability and blunted vascular oxidative stress, consequently reducing cardiac fibrosis and remodeling, arterial resistance, blood pressure, and endothelial dysfunction, consequently the health and life span was increased [2, 6, 29, 93-95]. These experimental data suggest that a decreased caloric apport would ameliorate concomitant pathologies and increase life span in old patients. However, some geriatric patients are frail and sarcopenic, and a caloric restriction would not be adequate.

Moreover, in well-developed countries overweight is an increasing problem, and it is well known that patients show limited adherence to long-term dietary recommendations and other lifelong lifestyle changes. Therefore, an alternative approach would be helpful, and a pharmacological approach could be an alternative. Since experimental studies [96] have detected that the positive effect of long-term caloric restriction is due to a reduction of age-related dysfunction of AMP-activated protein kinase, research searched for drugs that might reduce such dysfunction and would retard senescence with a similar effect as long-term caloric restriction [2, 6, 93]. The GLP-1 agonists semaglutide and tirzedapide effectively have favorable metabolic and cardiovascular effects while reducing the sensation of hunger and body weight. However, these drugs have been not studied for specific use in overweight or in the treatment of age-related disease aiming to increase life span. Using drugs to delay aging in healthy individuals is still controversial due to their potential long-term side effects, which may exceed the benefits [95]. It is established that senescence is essentially a cell fate, like differentiation, proliferation, apoptosis, and necrosis [2, 13, 23, 27, 43]. Based on this knowledge, in 2004/2005, a search began to find chemotherapeutics (*senolytics*), a new class of drugs that selectively kill senescent cells or suppress their disease-causing phenotypes (senomorphics/senostatics). It is hypothesized that senolytics may enhance health span and delay, prevent, or treat multiple chronic diseases, geriatric syndromes, and age-related declines in physical resilience [96]. Initial attempts aimed to create fusion proteins comprising a senescent cell surface-binding domain coupled to a toxin, compound library screens for candidates that eliminate senescent but not non senescent cells, and other approaches [2, 96]. These approaches were unsuccessful. However, since 2015, several naturally occurring senolytics (dasatinib, quercetin, fisetin, and navitoclax) have been identified and clinically tested [96]. Early data indicate that these senolytics alleviate disease in numerous organs, improve physical function and resilience, suppress all causes of mortality, even if administered to the aged, decrease senescent cells, reduce inflammation, and alleviate frailty in humans [96]. Clinical trials for diabetes, idiopathic pulmonary fibrosis, Alzheimer's disease, COVID-19, osteoarthritis, osteoporosis, eye diseases, bone marrow transplant, and childhood cancer survivors are beginning [96]. Unfortunately, there has been premature excitement about senolytics and efforts to sell them to the public, while safety and efficacy measures are still being evaluated [95, 96]. Until valid data are obtained from good studies, it is too early for senolytics to be used outside of clinical trials, and more information about safety, tolerability, side effects, and effectiveness in reducing senescent cell burden in humans is needed. Severe unanticipated side effects could emerge and physicians are concerned about prescribing senolytics or self-medication [95-98].

It should not be forgotten that aging is a heterogeneous process guided by epigenetic, genetic and environmental factors [2, 40-43]. Understanding the epigenetic mechanisms in aging could

provide new strategies to delay aging. Aging interventions based on manipulating epigenetic mechanisms have led to the alleviation of aging or the extension of the lifespan in animal models. various clinical trials for aging intervention are ongoing, providing more evidence of the safety and efficacy of these therapies [41].

As for gerontogenes, at present, it is impossible to interfere with genes regulating β-adrenoceptors. On the other hand, antisense oligonucleotides, monoclonal antibodies, and gene/base editing aimed to interfere with this culprit's APOE gene are giving promising results, at least in the therapy of late-onset Alzheimer's disease [44]. Also, optimizing FoxO3 activity in humans to increase lifespan and reduce age-related diseases represents an exciting avenue of clinical investigation [45]. Many experimental and some clinical observational studies outlined that the gerontogenes JunD, Klotho, mTOR, $p66^{shc}$, SHC1, and sirtuins play crucial roles in the occurrence of oxidative stress and age-related pathologies. Therefore, some therapies might be derived from interacting with these gerontogenes. Indeed, rapamycin interacted with the mTOR1 gene and protected the cardiovascular system, but its side effects preclude long-term use in patients [69, 70]. Resveratrol, which is naturally found in grape skin and red wine, targets many enzymes and is a potent SIRT1 activator. In an experiment, resveratrol protected mice against atherosclerosis, heart failure, and hypertension [6]. However, many unknowns hamper resveratrol's use in human medicine. Furthermore, it should be considered that the effects of SIRT genes on the age-related pathologies are insufficiently understood, because these gerontogenes may have positive and negative effects. Ongoing projects are assessing a possible therapy with drugs acting on the Klotho and $p66^{shc}$ genes, but at present few data are available.

In summary, strategies to promote healthy aging would benefit the individual and reduce the medical, sociological, and economic associated with the progressive aging of the world population and their age-related pathologies [2].

9. Conclusions

A rapidly increasing amount of data from longevity medicine, also considering epigenetics and genetics, his giving new research direction for understanding and treating age-related pathologies and increasing life span. Research has begun to validate and refine available data and identify more accurate and robust aging indicators. However, at present, *There are known knowns. There are things we know that we know. There are known unknowns. That is to say, there are things that we know that we don't know. But there are also unknown unknowns. There are things we don't know we don't know* (*Donald Rumsfeld)*. The road is long and most likely bumpy. It should also be recalled that antiaging interventions should focus on extending the health span rather than simply prolonging life [95].

Author Contributions

S. Pandolfi collected the references and checked the text. G. Cocco studied the references, wrote the manuscript and checked all corrections.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Vaupel JW, Villavicencio F, Bergeron Boucher MP. Demographic perspectives on the rise of longevity. Proc Natl Acad Sci. 2021; 118: e2019536118.
2. Wissler Gerdes EO, Zhu Y, Tchkonia T, Kirkland JL. Discovery, development, and future application of senolytics: Theories and predictions. FEBS J. 2020; 287: 2418-2427.
3. Gavrilov LA, Gavrilova NS. New developments in the biodemography of aging and longevity. Gerontology. 2015; 61: 364-371.
4. Bischof E, Scheibye Knudsen M, Siow R, Moskalev A. Longevity medicine: Upskilling the physicians of tomorrow. Lancet Health Longev. 2021; 2: e187-e188.
5. Jin K. Modern biological theories of aging. Aging Dis. 2010; 1: 72-74.
6. Puspitasari YM, Camici GG. Role of lifespan-regulating genes in age-related cardiovascular disease. Cardiovasc Med. 2021. Doi: 10.4414/cvm.2022.02146.
7. Harman D. Free radical theory of aging: History. Free Radicals and Aging. Basel, Switzerland: Birkhäuser Basel; 1992.
8. Harman D. The aging process: Major risk factor for disease and death. Proc Natl Acad Sci. 1991; 88: 5360-5363.
9. Kirkwood TB, Austad SN. Why do we age? Nature. 2000; 408: 233-238.
10. Dikalova A, Clempus R, Lassègue B, Cheng G, McCoy J, Dikalov S, et al. Nox1 overexpression potentiates angiotensin II-induced hypertension and vascular smooth muscle hypertrophy in transgenic mice. Circulation. 2005; 112: 2668-2676.
11. Münzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. Impact of oxidative stress on the heart and vasculature: Part 2 of a 3-part series. J Am Coll Cardiol. 2017; 70: 212-229.
12. Almeida AJ, Ribeiro TP, Medeiros IA. Aging: Molecular pathways and implications on the cardiovascular system. Oxid Med Cell Longev. 2017; 2017: 7941563.
13. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018; 9: 7204-7218.
14. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017; 2: 17023.
15. Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, et al. Immunosenescence and inflamm-aging as two sides of the same coin: Friends or foes? Front Immunol. 2018; 8: 1960.
16. Vita JA, Keaney Jr JF, Larson MG, Keyes MJ, Massaro JM, Lipinska I, et al. Brachial artery vasodilator function and systemic inflammation in the Framingham Offspring Study. Circulation. 2004; 110: 3604-3609.
17. Schnabel R, Larson MG, Dupuis J, Lunetta KL, Lipinska I, Meigs JB, et al. Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection. Hypertension. 2008; 51: 1651-1657.
18. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017; 377: 1119-1131.
19. Chung HY, Kim DH, Lee EK, Chung KW, Chung S, Lee B, et al. Redefining chronic inflammation in aging and age-related diseases: Proposal of the senoinflammation concept. Aging Dis. 2019; 10: 367-382.

20. Liu D, Richardson G, Benli FM, Park C, de Souza JV, Bronowska AK, et al. Inflammageing in the cardiovascular system: Mechanisms, emerging targets, and novel therapeutic strategies. Clin Sci. 2020; 134: 2243-2262.
21. Pepys MB. The pentraxins 1975-2018: Serendipity, diagnostics and drugs. Front Immunol. 2018; 9: 2382.
22. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000; 342: 836-843.
23. Hansson GK, Libby P. The immune response in atherosclerosis: A double-edged sword. Nat Rev Immunol. 2006; 6: 508-519.
24. C reactive protein coronary heart disease genetics collaboration (CCGC). Association between C reactive protein and coronary heart disease: Mendelian randomisation analysis based on individual participant data. BMJ. 2011; 342: d548.
25. Liu C, Li C. C-reactive protein and cardiovascular diseases: A synthesis of studies based on different designs. Eur J Prev Cardiol. 2023. Doi: 10.1093/eurjpc/zwad116.
26. Williams GC. Pleiotropy, natural selection, and the evolution of senescence: Evolution 11, 398-411 (1957). Sci Aging Knowledge Environ. 2001; 2001: cp13.
27. Harley CB. Telomere loss: Mitotic clock or genetic time bomb? Mutat Res. 1991; 256: 271-282.
28. Camici GG, Liberale L. Aging: The next cardiovascular disease? Eur Heart J. 2017; 38: 1621-1623.
29. Vidaček NŠ, Nanić L, Ravlić S, Sopta M, Gerić M, Gajski G, et al. Telomeres, nutrition, and longevity: Can we really navigate our aging? J Gerontol Ser A. 2018; 73: 39-47.
30. Steenstrup T, Kark JD, Verhulst S, Thinggaard M, Hjelmborg JV, Dalgård C, et al. Telomeres and the natural lifespan limit in humans. Aging. 2017; 9: 1130-1142.
31. Whittemore K, Vera E, Martínez Nevado E, Sanpera C, Blasco MA. Telomere shortening rate predicts species life span. Proc Natl Acad Sci. 2019; 116: 15122-15127.
32. Barrett EL, Richardson DS. Sex differences in telomeres and lifespan. Aging Cell. 2011; 10: 913-921.
33. Bischoff C, Petersen HC, Graakjaer J, Andersen Ranberg K, Vaupel JW, Bohr VA, et al. No association between telomere length and survival among the elderly and oldest old. Epidemiology. 2006; 17: 190-194.
34. Lindahl T. Instability and decay of the primary structure of DNA. Nature. 1993; 362: 709-715.
35. Bertram JS. The molecular biology of cancer. Mol Aspects Med. 2000: 21: 167-223.
36. de Souza Pinto NC, Hogue BA, Bohr VA. DNA repair and aging in mouse liver: 8-oxodG glycosylase activity increase in mitochondrial but not in nuclear extracts. Free Radic Biol Med. 2001; 30: 916-923.
37. Yousefzadeh MJ, Flores RR, Zhu YI, Schmiechen ZC, Brooks RW, Trussoni CE, et al. An aged immune system drives senescence and ageing of solid organs. Nature. 2021; 594: 100-105.
38. Kidd JM, Cooper GM, Donahue WF, Hayden HS, Sampas N, Graves T, et al. Mapping and sequencing of structural variation from eight human genomes. Nature. 2008; 453: 56-64.
39. Sen P, Shah PP, Nativio R, Berger SL. Epigenetic mechanisms of longevity and aging. Cell. 2016; 166: 822-839.
40. Moskalev A, Aliper A, Smit McBride Z, Buzdin A, Zhavoronkov A. Genetics and epigenetics of aging and longevity. Cell Cycle. 2014; 13: 1063-1077.

41. Wang K, Liu H, Hu Q, Wang L, Liu J, Zheng Z, et al. Epigenetic regulation of aging: Implications for interventions of aging and diseases. Signal Transduct Target Ther. 2022; 7: 374.
42. Mc Auley MT. An evolutionary perspective of lifespan and epigenetic inheritance. Exp Gerontol. 2023; 179: 112256.
43. Caruso C, Ligotti ME, Accardi G, Aiello A, Duro G, Galimberti D, et al. How important are genes to achieve longevity? Int J Mol Sci. 2022; 23: 5635.
44. Yang A, Kantor B, Chiba Falek O. Apoe: The new frontier in the development of a therapeutic target towards precision medicine in late-onset Alzheimer. Int J Mol Sci. 2021; 22: 1244.
45. Morris BJ, Willcox DC, Donlon TA, Willcox BJ. FOXO3: A major gene for human longevity-a mini-review. Gerontology. 2015; 61: 515-525.
46. Wikipedia. Epigenetic clock [Internet]. Wikipedia; 2023. Available from: https://en.wikipedia.org/wiki/Epigenetic_clock.
47. Crimi E, Benincasa G, Figueroa Marrero N, Galdiero M, Napoli C. Epigenetic susceptibility to severe respiratory viral infections and its therapeutic implications: A narrative review. Br J Anaesth. 2020; 125: 1002-1017.
48. Cocco G, Amiet P. Epigenetics and medicine. OBM Genet. 2021; 5: 133.
49. Napoli C, Benincasa G, Schiano C, Salvatore M. Differential epigenetic factors in the prediction of cardiovascular risk in diabetic patients. Eur Heart J Cardiovasc Pharmacother. 2020; 6: 239-247.
50. Cocco G. Immune senescence and Covid-19 pandemic. OBM Geriatr. 2020; 4: 132.
51. DiNardo AR, Netea MG, Musher DM. Postinfectious epigenetic immune modifications-a double-edged sword. N Engl J Med. 2021; 384: 261-270.
52. Gao XM, Agrotis A, Autelitano DJ, Percy E, Woodcock EA, Jennings GL, et al. Sex hormones and cardiomyopathic phenotype induced by cardiac β2-adrenergic receptor overexpression. Endocrinology. 2003; 144: 4097-4105.
53. Zhao L, Yang F, Xu K, Cao H, Zheng GY, Zhang Y, et al. Common genetic variants of the β2-adrenergic receptor affect its translational efficiency and are associated with human longevity. Aging Cell. 2012; 11: 1094-1101.
54. National Center for Biotechnology Information. JunD proto-oncogene, AP-1 transcription factor subunit [Homo sapiens (human)]. Bethesda, MD, US: National Center for Biotechnology Information; 2023; Gene ID: 3727. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=3727.
55. Paneni F, Osto E, Costantino S, Mateescu B, Briand S, Coppolino G, et al. Deletion of the activated protein-1 transcription factor JunD induces oxidative stress and accelerates age-related endothelial dysfunction. Circulation. 2013; 127: 1229-1240.
56. Diaz Cañestro C, Reiner MF, Bonetti NR, Liberale L, Merlini M, Wüst P, et al. AP-1 (activated protein-1) transcription factor JunD regulates ischemia/reperfusion brain damage via IL-1β (interleukin-1β). Stroke. 2019; 50: 469-477.
57. Paneni F, Diaz Cañestro C, Libby P, Lüscher TF, Camici GG. The aging cardiovascular system: Understanding it at the cellular and clinical levels. J Am Coll Cardiol. 2017; 69: 1952-1967.
58. HUGO Gene Nomenclature Committee. Symbol report for KL. Cambridge, UK: HUGO Gene Nomenclature Committee. HGNC: 6344. Available from: https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:6344.

59. Kuro o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature. 1997; 390: 45-51.
60. Saito Y, Yamagishi T, Nakamura T, Ohyama Y, Aizawa H, Suga T, et al. Klotho protein protects against endothelial dysfunction. Biochem Biophys Res Commun. 1998; 248: 324-329.
61. Lim K, Halim A, Lu TS, Ashworth A, Chong I. Klotho: A major shareholder in vascular aging enterprises. Int J Mol Sci. 2019; 20: 4637.
62. Corsetti G, Pasini E, Scarabelli TM, Romano C, Agrawal PR, Chen Scarabelli C, et al. Decreased expression of Klotho in cardiac atria biopsy samples from patients at higher risk of atherosclerotic cardiovascular disease. J Geriatr Cardiol. 2016; 13: 701-711.
63. Poelzl G, Ghadge SK, Messner M, Haubner B, Wuertinger P, Griesmacher A, et al. Klotho is upregulated in human cardiomyopathy independently of circulating Klotho levels. Sci Rep. 2018; 8: 8429.
64. Olejnik A, Krzywonos Zawadzka A, Banaszkiewicz M, Bil Lula I. Klotho protein contributes to cardioprotection during ischaemia/reperfusion injury. J Cell Mol Med. 2020; 24: 6448-6458.
65. University of California Santa Cruz. Human Gene MTOR (uc001asd.3) [Internet]. Santa Cruz, CA, US: University of California Santa Cruz. Available from: https://genome.ucsc.edu/cgi-bin/hgGene?db=hg19&hgg_gene=MTOR.
66. Fingar DC, Blenis J. Target of rapamycin (TOR): An integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. Oncogene. 2004; 23: 3151-3171.
67. Sciarretta S, Volpe M, Sadoshima J. Mammalian target of rapamycin signaling in cardiac physiology and disease. Circ Res. 2014; 114: 549-564.
68. Sciarretta S, Forte M, Frati G, Sadoshima J. New insights into the role of mTOR signaling in the cardiovascular system. Circ Res. 2018; 122: 489-505.
69. Joannidès R, Monteil C, De Ligny BH, Westeel PF, Iacob M, Thervet E, et al. Immunosuppressant regimen based on sirolimus decreases aortic stiffness in renal transplant recipients in comparison to cyclosporine. Am J Transplant. 2011; 11: 2414-2422.
70. Flynn JM, O'Leary MN, Zambataro CA, Academia EC, Presley MP, Garrett BJ, et al. Late-life rapamycin treatment reverses age-related heart dysfunction. Aging Cell. 2013; 12: 851-862.
71. UniProt. Q86YP4 · P66A_HUMAN [Internet]. UniProt; 2023. Available from: https://www.uniprot.org/uniprotkb/Q86YP4/entry#function.
72. Galimov ER. The Role of $p66^{shc}$ in Oxidative Stress and Apoptosis. Acta Naturae. 2010; 2: 44-51.
73. Berry A. Cirulli F. The $p66^{shc}$ gene paves the way for healthspan: Evolutionary and mechanistic perspectives. Neurosci Biobeghav Rev. 2013; 3: 790-802.
74. Francia P, delli Gatti C, Bachschmid M, Martin Padura I, Savoia C, Migliaccio E, et al. Deletion of $p66^{shc}$ gene protects against age-related endothelial dysfunction. Circulation. 2004; 110: 2889-2895.
75. Napoli C, Martin Padura I, de Nigris F, Giorgio M, Mansueto G, Somma P, et al. Deletion of the $p66^{shc}$ longevity gene reduces systemic and tissue oxidative stress, vascular cell apoptosis, and early atherogenesis in mice fed a high-fat diet. Proc Natl Acad Sci. 2003; 100: 2112-2116.
76. Spescha RD, Shi Y, Wegener S, Keller S, Weber B, Wyss MM, et al. Deletion of the ageing gene $p66^{shc}$ reduces early stroke size following ischaemia/reperfusion brain injury. Eur Heart J. 2013; 34: 96-103.

77. Spescha RD, Klohs J, Semerano A, Giacalone G, Derungs RS, Reiner MF, et al. Post-ischaemic silencing of p66^{shc} reduces ischaemia/reperfusion brain injury and its expression correlates to clinical outcome in stroke. Eur Heart J. 2015; 36: 1590-1600.
78. Camici GG, Cosentino F, Tanner FC, Lüscher TF. The role of p66^{shc} deletion in age-associated arterial dysfunction and disease states. J Appl Physiol. 2008; 105: 1628-1631.
79. Franzeck FC, Hof D, Spescha RD, Hasun M, Akhmedov A, Steffel J, et al. Expression of the aging gene p66^{shc} is increased in peripheral blood monocytes of patients with acute coronary syndrome but not with stable coronary artery disease. Atherosclerosis. 2012; 220: 282-286.
80. Miao Q, Wang Q, Dong L, Wang Y, Tan Y, Zhang X. The expression of p66shc in peripheral blood monocytes is increased in patients with coronary heart disease and correlated with endothelium-dependent vasodilatation. Heart Vessel. 2015; 30: 451-457.
81. Liberale L, Kraler S, Camici GG, Lüscher TF. Ageing and longevity genes in cardiovascular diseases. Basic Clin Pharmacol Toxicol. 2020; 127: 120-131.
82. Wikipedia. UCSC Genome Browser [Internet]. Wikipedia, 2023. Available from: https://en.wikipedia.org/wiki/UCSC_Genome_Browser.
83. Xu S, Bai P, Jin ZG. Sirtuins in cardiovascular health and diseases. Trends Endocrinol Metab. 2016; 27: 677-678.
84. Ravi V, Mishra S, Sundaresan NR. Role of sirtuins in cardiovascular diseases. In: SIRTUIN BIOLOGY IN MEDICINE. Targeting New Avenues of Care in Development, Aging, and Disease. London, UK: Academic Press; 2021. pp. 261-264.
85. Stein S, Schäfer N, Breitenstein A, Besler C, Winnik S, Lohmann C, et al. SIRT1 reduces endothelial activation without affecting vascular function in ApoE-/-mice. Aging. 2010; 2: 353-360.
86. Winnik S, Stein S, M Matter C. SIRT1-an anti-inflammatory pathway at the crossroads between metabolic disease and atherosclerosis. Curr Vasc Pharmacol. 2012; 10: 693-696.
87. Winnik S, Auwerx J, Sinclair DA, Matter CM. Protective effects of sirtuins in cardiovascular diseases: From bench to bedside. Eur Heart J. 2015; 36: 3404-3412.
88. Hsu CP, Zhai P, Yamamoto T, Maejima Y, Matsushirma S, Hariharan N, et al. Silent information regulator 1 protein protects the heart from ischemia/reperfusion. Circulation 2010; 122: 2170-2182.
89. Chen X, Lu W, Wu D. Sirtuin 2 (SIRT2): Confusing roles in the pathophysiology of neurological disorders. Front Neurosci. 2021; 15. Doi: 10.3389/fnins.2021.614107.
90. Winnik S, Gaul DS, Preitner F, Lohmann C, Weber J, Miranda MX, et al. Deletion of Sirt3 does not affect atherosclerosis but accelerates weight gain and impairs rapid metabolic adaptation in LDL receptor knockout mice: Implications for cardiovascular risk factor development. Basic Res Cardiol. 2014; 109: 399.
91. Diaz Cañestro C, Merlini M, Bonetti NR, Liberale L, Wüst P, Briand Schumacher S, et al. Sirtuin 5 as a novel target to blunt blood-brain barrier damage induced by cerebral ischemia/reperfusion injury. Int J Cardiol. 2018; 260: 148-155.
92. Gaul DS, Weber J, Van Tits LJ, Sluka S, Pasterk L, Reiner MF, et al. Loss of Sirt3 accelerates arterial thrombosis by increasing formation of neutrophil extracellular traps and plasma tissue factor activity. Cardiovasc Res. 2018; 114: 1178-1188.

93. Donato AJ, Walker AE, Magerko KA, Bramwell RC, Black AD, Henson GD, et al. Life-long caloric restriction reduces oxidative stress and preserves nitric oxide bioavailability and function in arteries of old mice. Aging Cell. 2013; 12: 772-783.
94. Alfaras I, Di Germanio C, Bernier M, Csiszar A, Ungvari Z, Lakatta EG, et al. Pharmacological strategies to retard cardiovascular aging. Cardiovasc Res. 2016; 118: 1626-1642.
95. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological versus chronological aging: JACC focus seminar. J Am Coll Cardiol. 2020; 75: 919-930.
96. Kirkland JL, Tchkonia T. Senolytic drugs: From discovery to translation. J Int Med. 2020; 288: 518-536.
97. Robbins PD, Jurk D, Khosla S, Kirkland JL, LeBrasseur NK, Miller JD, et al. Senolytic drugs: Reducing senescent cell viability to extend health span. Annu Rev Pharmacol Toxicol. 2021; 61: 779-803.
98. Lagoumtzi SM, Chondrogianni N. Senolytics and senomorphics: Natural and synthetic therapeutics in the treatment of aging and chronic diseases. Free Radic Biol Med. 2021; 171: 169-190.