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REVIEW ARTICLE

Aging and age-related diseases: from mechanisms to therapeutic strategies

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Abstract Aging is a physiological process mediated by numerous biological and genetic pathways, which are directly linked to lifespan and are a driving force for all age-related diseases. Human life expectancy has greatly increased in the past few decades, but this has not been accompanied by a similar increase in their healthspan. At present, research on aging biology has focused on elucidating the biochemical and genetic pathways that contribute to aging over time. Several aging mechanisms have been identified, primarily including genomic instability, telomere shortening, and cellular senescence. Aging is a driving factor of various age-related diseases, including neurodegenerative diseases, cardiovascular diseases, cancer, immune system disorders, and musculoskeletal disorders. Efforts to find drugs that improve the healthspan by targeting the pathogenesis of aging have now become a hot topic in this field. In the present review, the status of aging research and the development of potential drugs for aging-related diseases, such as metformin, rapamycin, resveratrol, senolytics, as well as caloric restriction, are summarized. The feasibility, side effects, and future potential of these treatments are also discussed, which will provide a basis to develop novel anti-aging therapeutics for improving the healthspan and preventing aging-related diseases.

Keywords Aging · Hallmarks of aging · Age-related diseases · Anti-aging drugs

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Introduction

Since the dawn of human civilization, the desire for immortality has been a common pursuit. Due to improvements in living conditions and the continuous development of medical technology, human lifespan has increased dramatically over the last century (Campisi et al. 2019). Aging is the irreversibly progressive decline of physiological function, which eventually leads to age-related diseases, such as cardiovascular diseases, musculoskeletal disorders and arthritis, neurodegenerative diseases, and cancer. These age-related diseases produce a heavy economic and psychological burden for patients, their families, and society as a whole (de Magalhães et al. 2017). The

primary feature of aging is the accumulation of cellular senescence (López-Otín et al. 2013) induced by destructive stimuli from inside and outside the cell (Hernandez-Segura et al. 2018). Cellular senescence affects the body in two ways. Firstly, excessive accumulation of senescent cells inevitably affects tissue regeneration. Secondly, senescent cells secrete a large number of inflammatory factors and present with the senescence-associated secretory phenotype (SASP), which has negative effects on the surrounding environment (López-Otín et al. 2013; Baker et al. 2016) found that although AP20187, a synthetic drug that activates FK506-binding protein-fused Casp8, effectively cleared senescent cells with high expression of p16 (Ink4a) and prolonged the lifespan of mice, some of the mice had elevated urea levels and exhibited severe thrombocytopenia (Baker et al. 2016). Bael et al. (2018) found that WM-1119, an inhibitor of the histone acetyltransferases KAT6A and KAT6B, could induce cellular senescence and arrest tumor growth in mice with lymphoma. Silva-Álvarez et al. (2020) found that the removal of senescent cells from adult zebrafish with limb amputation injuries was harmful to tissue regeneration (Da Silva-Álvarez et al. 2020). Thus, blocking cellular senescence may cause other complications. Therefore, cellular senescence is a double-edged sword when it comes to maintaining cellular balance.

Many strategies for ameliorating age-related diseases have been extensively studied, including calorie restriction through the control of diet and exercise and pharmaceutical treatments targeting specific cells and molecules (Di Daniele et al. 2017; Leong 2018). Although these treatments have achieved significant effects in various models, medication for the elderly is still a challenging issue that needs careful attention. This is because insufficient clinical data indicate that these drugs have a positive effect. On the other hand, careful consideration must also be given to the possible negative effects of these drugs. In this review, the mechanisms of aging will be described, several aging-related diseases will be identified to demonstrate the possible consequences of aging, and an analysis of the feasibility of targeted aging therapies will be performed to pave the way for future research on aging biology.

Hallmarks of aging

In order to illuminate the mechanisms and effects of anti-aging therapies on aging-related diseases, the cellular and molecular markers for aging must first be clarified. Based on the study of many different types of organisms, especially mammals, nine factors and related candidate markers are usually considered when determining the aging phenotype (López-Otín et al. 2013).

Genomic instability

One commonly accepted cause of aging is the accumulation of genetic damage, which could disrupt cell homeostasis and result in genome instability (Kubben and Misteli 2017). Somatic mutations, chromosomal aneuploidy, and copy mutations all contribute to exacerbating damage to the DNA (Tiwari and Wilson 2019). As humans age, defects appear in the DNA repair mechanism, which affects the expression of essential genes and the transcription pathways, leading to cell dysfunction. A large number of preclinical studies indicate that damaged DNA repair capability can lead to the occurrence of premature aging syndromes, such as Werner syndrome and Bloom syndrome (Foo et al. 2019). In addition, mutations in aged mitochondrial DNA and deficits in the nuclear lamina can also cause genome instability (Kauppila et al. 2018). Genome damage is closely related to aging, so interventions that can stabilize the genome and restore DNA repair capabilities should be explored to define its impact on aging.

Reduced telomere length

Telomeres are repetitive sequences at the distal ends of chromosomes. If telomeres reach a critically short length during cell division, known as the Hayflick limit, it triggers DNA damage and cellular senescence (Hayflick and Moorhead 1961; Herrmann et al. 2018). Importantly, telomere shortening also shows during natural aging in both humans and mice (Zhu et al. 2019). Also, numerous epidemiological studies have indicated that telomere depletion was significantly correlated to aging, biological morbidity, and mortality (Mensà et al. 2019). Telomerase, which is highly expressed in embryonic stem cells to extend telomeres, cannot be detected in most normal human cells

(Saretzki 2018). Ullah et al. (2019) found that impaired telomerase activity accelerated senescence of stem cells (Ullah and Sun 2019). Jesus et al. (2012) reported that activation of telomerase activity through viral transduction could extend the survival time and reduce the incidence of cancer in wild-type mice (de Jesus et al. 2012). Notably, cells with short telomeres may escape senescence and become immortalized, usually by activating or upregulating telomerase. However, most human cancers have shorter telomeres and increased activity of telomerase (Shay 2016). Or it can be thought of in another way that the senescence caused by the shorter telomeres and limited telomerase activity may be the mechanism that prevents tumorigenesis in some large and long-lived mammals. There are several telomerase inhibitors in clinical phase II trials for the treatment of various cancers (Shay 2016). Telomere shortening can cause mammalian aging, while telomerase can reverse this phenomenon. Therefore, telomerase and its regulation of telomere length are important therapeutic targets for cancer and age-related diseases. Therefore, targeting telomeres or telomerase may be a strategy for developing innovative drug therapies to delay aging.

Epigenetic alterations

Modifications of chromatin include alterations in DNA methylation, histone modifications, and chromatin remodeling, which are related to cell aging (Kane and Sinclair 2019). Sirtuin families have been studied extensively as potential anti-aging factors. Ravi et al. (2019) reported that SIRT6 gene deletion severely affects cardiac function in mice and that inhibition of mTOR or Sp1 can eliminate the negative effects of SIRT6 gene deletion (Ravi et al. 2019). In addition, SIRT1 and SIRT3 genes all contribute to the improvement of healthy aging in mammals (Morigi et al. 2018). With aging, mammalian cells undergo global and local DNA hypomethylation (Kane and Sinclair 2019). Maierhofer et al. (2019) confirmed that DNA methylation and histone modifications were increased in mouse models of the premature aging syndrome (Maierhofer et al. 2019). However, there is still no evidence that DNA methylation can be changed to prolong life. It was shown that epigenetic changes could be reversed to some extent (Chen and Kerr 2019). Azacitidine and decitabine are epigenetic modifiers that have been approved by the FDA for treating myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). In clinical trials, both compounds have been shown to improve patients' pathology results while extending their average life expectancy (Kantarjian et al. 2012). Overall, understanding and manipulating the epigenome holds promise for improving age-related pathologies and extending a healthy lifespan.

Loss of proteostasis

The occurrence of aging and most aging-related diseases are related to the impairment of protein homeostasis. Protein aggregation, post-translational modification, and altered protein turnover are hallmarks of aging (Basisty et al. 2018). Autophagy and the ubiquitin-proteasome system are the primary protein degradation systems of the cells (Kaushik and Cuervo 2015; Klaips et al. 2018), and their activity declines with aging. Studies showed that the autophagy activators, such as rapamycin and spermidine, could extend the lifespan of yeast, nematodes, fruit flies, and mice (Wong et al. 2020). In addition, reducing protein synthesis by inhibiting the mTOR signaling pathway and calorie restriction also prolongs the lifespan (Basisty et al. 2018). Sorrentino et al. (2017) reported that maintaining protein homeostasis could reduce the aggregation of amyloid protein in Alzheimer's disease (AD) transgenic nematodes and mice and increased the lifespan of the test animals to a certain extent (Sorrentino et al. 2017). Collectively, studies on protein synthesis, quality control, and degradation pathways strongly suggest that maintenance of proteostasis is essential for health and longevity.

Deregulated nutrient sensing

Nutrient sensing through insulin/IGF-1 (IIS) was the first pathway demonstrated to regulate aging and age-related diseases in organisms. Pharmacological or caloric restriction (CR) targeting nutrient signaling pathways have been shown to attenuate aging in many organisms (Santos et al. 2016). Attenuating the signaling activity of the IIS pathway consistently extended the lifespan (Mathew et al. 2017). Bitto et al. (2016) stated that transient rapamycin treatment could inhibit the mTOR signaling pathway, thereby extending the lifespan of middle-aged mice (Bitto et al.

2016). Downregulation of mTORC1 expression also improved the average lifespan of yeast, elegans, and fruit flies (Arriola Apelo and Lamming 2016). The other two sensors in the IIS axis are AMPK and sirtuins. Emerging studies have demonstrated that metformin could activate the AMPK signaling pathway to extend the lifespan. Salminen et al. (2017) found that fibroblast growth factor 21 (FGF21) could extend the lifespan of mammals by activating AMPK signaling (Salminen et al. 2017). Studies also showed that CR could extend the lifespan of these model organisms by regulating the sirtuin family (Kapahi et al. 2017). Therefore, the synthesis and decomposition pathways of nutrient metabolism should be considered for targeted anti-aging therapies. Meanwhile, the complexity of certain signal pathways should also be deliberated. For example, the inhibition of mTOR will cause slow wound healing, insulin resistance, and other adverse reactions such as induced cataracts (Zaza et al. 2018).

Cellular senescence

Cellular senescence is a state of cell cycle arrest (Hernandez-Segura et al. 2018). The general view holds that aging is caused by a large accumulation of senescent cells in the tissue. The senescence-related secreted phenotype (SASP) and DNA damage are the main factors leading to senescence (Hernandez-Segura et al. 2017). In addition, mitochondrial dysfunction-associated senescence (MiDAS) is associated with mild or no transcriptional induction of several SASP factors (Wiley et al. 2016). For instance, inhibition of the IL-1 receptor reduced the expression of SASP and partially prevented oncogene-induced senescence (OIS) (Acosta et al. 2013). At the same time, many SASP factors exert non-cell-autonomous function and cause neighboring cells to age (Acosta et al. 2008; Ritschka et al. 2017). The critical role of $p16^{INK4a}$ and p53 in the induction of cell senescence has favored the hypothesis that they contribute to physiological aging (López-Otín et al. 2013). Cao et al. (2003) showed that the aging status of premature mutant mice can be significantly reduced by eliminating $p16^{INK4a}$ or p53, which was consistence with the findings of other groups (Baker et al. 2011; Cao et al. 2003). However, mice with a mild and systemic increase in $p16^{INK4a}$, $p19^{ARF}$, or p53 tumor suppressors exhibited an extended lifespan (Matheu et al. 2007). However, it is worth noting that cellular senescence can also be beneficial. In fact, senescence is a potent anti-cancer mechanism that, as mentioned earlier, can prevent malignancy by limiting the replication of preneoplastic cells in the early stage. Several drugs, such as docetaxel, bleomycin, cyclophosphamide, doxorubicin, that are used in the clinical treatment of cancer are formally based on this feature of cellular aging known as therapy-induced senescence (TIS) (Calcinotto et al. 2019). In summary, cell senescence is a double-edged sword, which can either present a beneficial compensatory response to damage, or accelerate aging by exhausting tissue regeneration. Therefore, it is necessary to consider these two processes when developing new interventions.

Stem cell exhaustion

The loss of regenerative ability in tissues and organs is also one of the important features that cause aging. For example, with advancing age, the activity of hematopoietic stem cells decreases, which can lead to a series of pathological manifestations, such as a reduced adaptive immune response, an increased risk of anemia, and a decreased number of lymphoid cells (Goodell and Rando 2015). The same problem occurs in intestinal stem cells (ISCs). Compared with young mice, the number of ISCs in older mice is maintained at a lower level, resulting in a breakdown in intestinal structure and function (Keyes and Fuchs 2018). An important debate regarding the decline in stem cell function is the relative role of cell-intrinsic compared to cell-extrinsic pathways (Conboy and Rando 2012). Transplantation of muscle-derived stem cells from young mice to progeroid mice extended their lifespan and improved tissue function even though donor cells were not detected, suggesting that their therapeutic benefit may derive from systemic effects caused by secreted factors (Lavasani et al. 2012). Furthermore, using a parabiosis model, it has been demonstrated that the decline in neural and muscle stem cell function in old mice can be reversed by systemic factors from young mice (Xiong et al. 2018). Overall, targeting the senescence of stem cells has become a challenging problem that may provide novel concepts for therapeutic intervention.

Mitochondrial dysfunction

Mitochondria dysfunction could cause a deficit in the respiratory chain, increased reactive oxygen species (ROS) production, reduced ATP levels (Green et al. 2011; Harman 1965), promote apoptosis and trigger inflammation, which causes a variety of age-related diseases. However, numerous studies have shown that increased mitochondrial ROS production and oxidative damage cannot reduce the lifespan of model organisms (Kauppila et al. 2017). This is because it is only when the ROS level exceeds a certain threshold that age-related damage is aggravated (Hekimi et al. 2011). Hood et al. (2019) pointed out that an imbalance in the mitochondrial network and impaired mitochondrial function will lead to an imbalance in the metabolic state of skeletal muscle and a decrease in muscle mass. Exercise can slow the aging process caused by mitochondrial imbalance (Hood et al. 2019). However, it is still uncertain whether improving mitochondrial function can delay aging and prevent or treat age-related diseases.

Altered intercellular communication

Cellular communication also plays an important role in the aging process by regulating neuroendocrine, endocrine, and neuronal levels (Diamanti-Kandarakis et al. 2017). Neurohormonal signalings (e.g., renin-angiotensin, adrenergic, and insulin-IGF1 signaling) tend to mediate aging as inflammatory reactions increase, and the immunosurveillance environment changes (Salminen et al. 2012). Inflammation could be caused by the accumulation of proinflammatory cytokine secretion in senescent cells, an altered autophagy response, and increased NF-κB signaling (Green et al. 2011; Salminen et al. 2012; Senovilla et al. 2012). Genetic and pharmacological inhibition of NF-κB signaling could prevent age-related features in aging mouse models (Osorio et al. 2012). Inflammation and stress can activate the NF-κB signaling pathway in the hypothalamus, resulting in reduced GnRH. GnRH treatment can prevent impaired neurogenesis and slow down the aging process in mice (Zhang et al. 2013). Similar results also occurred in sirtuins. Pharmacological activation of SIRT1 may prevent inflammation in mice (Gillum et al. 2011). SIRT2 and SIRT6 also down-regulate inflammation through deacetylating NF-κB subunits and suppressing the downstream target genes (Kawahara et al. 2009; Yuan et al. 2016). In addition, cellular senescence influences neighboring cells via gap-junction contacts, growth factors, interleukins, and ROS, highlighting the importance of the microenvironment in modulating aging at different levels (Nelson et al. 2018). A large number of studies have shown that the change in intercellular communication is closely related to senescence. In a recent follow-up study, metformin significantly inhibited the expression of pro-inflammatory cytokines and reduced the associated risk of death in elderly diabetic patients (Tizazu et al. 2019). In primary hepatocytes, metformin inhibits TNF-α-dependent NF-κB signaling and the expression of IL-6 and IL-1β by its unique anti-hyperglycemic mechanism (Cameron et al. 2016; Moiseeva et al. 2013). Resveratrol could also significantly reduce the peripheral secretion of inflammatory factors in patients with grade one hypertension by improving intercellular communication (Li et al. 2018). As such, cellular senescence interferes with tissue homeostasis and regeneration and is responsible for aging-related diseases (van Deursen 2014). On the other hand, senescent cells can also play an active role in embryogenesis and tissue remodeling. For example, senescence is an effective barrier against tumorigenesis (Calcinotto et al. 2019). In the following, age-related diseases associated with cellular senescence and the potential targets of anti-aging drugs, from a theoretical basis of the mechanisms behind aging-related diseases, will be discussed.

Age-related diseases

Aging is the driving factor of various age-related diseases, and it causes a significant burden on social and economic stability. Based on the study of the Global Burden of Disease in 2017(GBD 2017), 92 of 293 (31.4%) diseases were determined to be age-related (Lublóy 2020). The most common aging-related diseases included neurodegenerative diseases, cancer, cardiovascular diseases, and metabolic diseases.

Neurodegenerative diseases

Aging is the most common risk factor for the development of neurodegenerative diseases.

Alzheimer's disease (AD) is the most common neurodegenerative disease in the world, and its incidence increases with advancing age (Trevisan et al. 2019). The characteristics of AD include extracellular amyloid plaques, intracellular neurofibrillary tangles (NFTs), and hyperphosphorylation of Tau protein (Xia et al. 2018; Janczura et al. 2018). Janczura et al. (2018) and Graff et al. (2012) found that histone acetylation was significantly reduced in the brains of AD patients and mice. Indirectly enhancing histone acetylation by chronic inhibition of histone deacetylases (HDACs) was able to reverse the cognitive deficits in a mouse model of AD (Kilgore et al. 2010). Aged mice and humans have a reduction in the number of neurons compared to their younger counterparts (Donev et al. 2009; Fabricius et al. 2013). Also, brain aging is mainly manifested by a large panel of pro-inflammatory factors characterized by SASP, altered signaling, and the accumulation of senescent glia (Harry 2013). The role of microglia in AD pathogenesis is complex (Wyss-Coray and Rogers 2012). Normally, microglia plays the role of a "scavenger", which is the main phagocytic cell in the brain, and performing a central role in the clearance of Aβ. However, the effectiveness of this clearance decreases with the development of AD (Njie et al. 2012; Olah et al. 2018) reported elderly microglia to have a more inflammatory phenotype (Olah et al. 2018). These findings showed that aged microglia presented both impaired neuroprotective abilities and low-grade neuroinflammation, but sustained secretion of the SASPs that drive inflammation in neurodegeneration. Additionally, reactive astrocytes are induced in various human neurodegenerative diseases, including AD (Liddelow and Barres 2017). Also, the number and the neurogenesis capability of neural stem cells (NSCs) decreases with age (Apple et al. 2017; Fan et al. 2017). Conversely, transplantation of NSCs slows the progression and restores spatial memory ability in AD mice (Zhang et al. 2017).

Parkinson's disease (PD) is also a neurodegenerative disease (Jankovic and Kapadia 2001). The prevalence of PD increases significantly, by approximately ten times, between 50 and 80 years of age (Pringsheim et al. 2014). The loss of dopaminergic neurons in the substantia nigra (SN) is considered a hallmark of PD (Kanaan et al. 2007). Several studies have shown that PD has the same cell function impairment seen in the aging process. The ubiquitin-proteasome system and lysosome in the brains of people with PD were mutated and showed histological signs of impaired function (Jankovic and Kapadia 2001). In addition, microglia cells showed increased staining intensity and transformation to activate phagocytic morphology during senescence, which occurs preferentially in the vulnerable vtSN region in PD. Compared to other sub-regions, the vtSN in elderly monkeys showed an excessively large microglia response, suggesting that the vtSN is more prone to neuroinflammation after being injured (Kanaan et al. 2008).

Cardiovascular disease

Aging has a significant effect on the heart and arterial system, leading to an increased prevalence of cardiovascular diseases (CVD), such as atherosclerosis, hypertension, myocardial infarction, and stroke (Donato et al. 2018). By 2030, about 20% of the population will be over 65 years old, and CVD will cause 40% of all deaths (Heidenreich et al. 2011). Aging cardiovascular tissues demonstrate pathological alterations, including hypertrophy, altered left ventricular (LV) diastolic function, diminished LV systolic reserve capacity, increased arterial stiffness, and impaired endothelial function (Lakatta and Levy 2003). Telomere shortening is related to the occurrence of CVD, vascular cell aging, aortic valve stenosis, cardiovascular risk factors (i.e., hypertension, type 2 diabetes, obesity, and smoking), and arterial thrombotic events. However, the causality of these associations remains uncertain (Kurz et al. 2006). The age-dependent deficiency of adrenergic signal transduction and calcium treatment, which are associated with cell aging, can also cause incompetence and reduced muscle strength of the LV, and affects exercise endurance (Paneni et al. 2017). The age-dependent changes to mitochondrial adaptor $p66^{Shc}$ profoundly affect the steady-state of the cardiovascular system. Clinical studies have shown that p66 Shc expression is significantly increased in stroke patients (Spescha et al. 2013, 2015) also confirmed that the production of ROS in the brain of p66 Shc-deficient mice was reduced, and the size of stroke was reduced after ischemia-reperfusion brain injury (Spescha et al. 2013). Genome instability is also a risk factor for CVD. Hutchinson–Gilford progeria syndrome, characterized by massive nuclear DNA

damage, is associated with premature atherosclerosis and CVD, which leads to fatal myocardial infarction (MI) or stroke by age 13 on average (Capell et al. 2007). In addition, abnormal epigenetic modifications also affect the incidence of CVD. SIRT6 can prevent endothelial dysfunction and atherosclerosis (Xu et al. 2016). SIRT1 overexpression improves the metabolic efficiency and endothelial function of aged mice (Winnik et al. 2015). The dysregulation of angiogenic pathways is associated with age-dependent reductions in the number and functionality of stem, and progenitor cells, including circulating angiogenic cells (CACs) and bone marrow (BM) derived cells (Lähteenvuo and Rosenzweig 2012).

Cancer

From 2010 to 2030, the aging of the US population will lead to a 67% increase in the incidence of cancer among Americans over 65 years of age (Smith et al. 2009). With the accumulation of senescent cells, the expression of SASP will increase and promote an inflammatory state, enhancing the invasive capabilities and accelerating the progression of cancer (Faget et al. 2019; Hartley et al. 2017). NF-κB and p38MAPK signaling pathways play important roles in the release of SASPs, which promote epithelial-mesenchymal transition (EMT) in cancer cells (Coppé et al. 2010). Epigenetic modification is an important link between aging and cancer. Aberrant methylation patterns are observed in almost all neoplasms. For example, $p21^{WAF1\ /\ CIP1}$, $p16^{INK4a}$, and the hypermethylation of these genes could drive carcinogenesis (Baylin and Ohm 2006; Li and Tollefsbol 2010). Fraga et al. (2005) found that cancer cells often exhibit losses in both histone acetylation and methylation, especially in H4 at the acetylated Lys16 and trimethylated Lys20 residues (Fraga et al. 2005). Histone acetyl dehydrogenase (HDAC) is closely related to the progression and prognosis of certain types of cancer, such as urogenital, reproductive, and gastrointestinal cancers (Li and Seto 2016). Histone deacetylase inhibitors (HDACi), such as MS-275 and SAHA, could trigger the apoptosis of advanced thyroid cancer by inhibiting HDAC1 and HDAC2 (Lin et al. 2019; Ma et al. 2019).

Immune system diseases

The immune system also undergoes dramatic aging-related changes, which could cause the body to lose its ability to fight against infection and cancer and increase the risk of autoimmune diseases (Sadighi Akha 2018). The decline of the immune system is characterized by a shift in T-cell phenotype from native to memory, fewer early progenitor B cells, an increased proportion of mature T-cells, as well as chronic low-grade inflammation (Ray and Yung 2018). Naïve $CD4^+$ T cells isolated from older humans and mice showed lower responsiveness to T-cell receptor stimulation and altered cytokine secretion profiles compared with Naïve $CD4^+$ T cells isolated from young hosts. Also, the function of naïve $CD4^+$ T cells to produce antibodies against B cells was reduced (Pereira et al. 2020; Raphael et al. 2020). However, age-dependent changes in the composition of memory $CD4^+$ T cell subsets also imply a weakened immune response to viral infections (e.g., influenza virus and vaccines) (Gustafson et al. 2020). One of the hallmarks of age-related changes in the human immune system is the accumulation of $CD28^-$ $CD8^+$ T cells, which are absent in neonates and constitute the majority (80–90%) of circulating $CD8^+$ T cells in the elderly. Accumulation of CD28-CD8 + T cells has also been found in viral infections such as COVID-19, which explains why the majority of patients with severe cases of COVID-19 are elderly (Pietrobon et al. 2020). In addition, naive CD4 + T cells had longer telomeres than memory CD4+T cells, and the difference in telomere length may reflect the number of cell divisions experienced by memory cells in vivo (Patrick and Weng 2019). Rufer et al. (1999) reported that telomere shortening was also found to occur during the transition from naïve to memory CD8 + T cells (Rufer et al. 1999). The aging lung is not only less functional, but it also has a reduced ability to prevent infections from environmental stresses and injuries. The aging of immune cells may lead to the development of disease. Th17 cells are predominantly observed in elderly asthmatics, in contrast to the Th2 inflammatory milieu presented in most young patients. Since Th17 cells can develop from the same lineage as anti-inflammatory regulatory T cells (Tregs), a preferential shift toward a Th17 response may reduce Tregs and promote the development of a pro-inflammatory environment in the elderly

(Bullone and Lavoie 2017; Diller et al. 2016; Doe et al. 2010).

Musculoskeletal disorders

The elderly are prone to injuries and degenerative musculoskeletal disorders. Sarcopenia and osteoarthritis (OA) are among the most common aging-related musculoskeletal disorders and have a significant economic impact (Grote et al. 2019). Sarcopenia is defined as the loss of muscle mass and function with age. Skeletal muscle mass and function decline by 30–50% by age 80, with the degree of muscle mass loss being worse in the elderly who are inactive. Increased inflammation leads to further ROS generation in skeletal muscles, which increases cell apoptosis and affects skeletal muscle catabolism (Musci et al. 2020). Impaired mitochondrial function and weakened antioxidant defenses have also been found to be associated with the development of sarcopenia (Gaffney et al. 2018). In addition, a growing number of studies have linked neuromuscular remodeling to muscle atrophy. Sheth et al. (2018) found that a decline in the number of motor units occurs before the loss of muscle function, which is due to reduced muscle size and contractility (Sheth et al. 2018). IL-6 inhibition is an approved and clinically effective therapy for rheumatoid arthritis (Favalli 2020). However, Costa et al. found that IL-6 knockout mice developed more severe symptoms of OA in old age, which suggests that OA is mediated by a combination of pro- and anti-inflammatory factors (da Costa et al. 2016). Spectral tracing experiments in mice have shown that the loss of chondrocytes proliferation activities due to aging may contribute to the progression of OA (Kozhemyakina et al. 2015). Accumulated DNA damage and oxidative stress also accelerate OA, and Didier et al. found that miR-24 inhibition of $p16^{INK4A}$ expression prevented chondrocyte senescence (Philipot et al. 2014). In addition, OA-associated reductions in AMPK activity have been observed in aged mice, and this reduced activity indicated a significant reduction in mitochondrial biogenesis (Wang et al. 2015; Caramés et al. 2015) demonstrated a significant decrease in autophagy protein expression due to decreased AMPK activity, resulting in increased levels of apoptosis and cartilage deficit in OA mice (Caramés et al. 2015). In summary, interventions to remove senescent cells and slow down cellular senescence can be considered for treating musculoskeletal disorders such as sarcopenia and OA in the elderly.

Anti-aging drugs

Anti-aging is a very promising and yet challenging field, which is complicated by the mechanisms of aging. Some FDA approved drugs target one or more molecules to reduce cellular damage and prolong the healthspan. Next, this review will examine examples of the data obtained for these drugs in different model organisms and clinical trials to promote future directions for the continued study of aging biology. In addition, some of the possible side effects of these drugs in humans and animal models will be discussed.

Metformin

Metformin is a widely prescribed medication, which has been used to treat type 2 diabetes (T2D) in the past century (Pryor and Cabreiro 2015). At the same time, metformin has been shown to effectively reduce the pathogenesis and mortality of cardiovascular diseases (Palmer et al. 2016). Compared with other hypoglycemic drugs, elderly patients taking metformin have a lower risk of death due to cardiovascular disease (Schlender et al. 2017). In addition, recent studies have found that metformin has a positive effect on cancer, neurodegenerative diseases, and polycystic ovary syndrome (Barzilai et al. 2016). For example, metformin leads to decreased insulin levels and IGF-1 signaling (Liu et al. 2011), activation of AMPK (Cho et al. 2015), inhibition of mTOR (Nair et al. 2014; Pérez-Revuelta et al. 2014), a reduction in ROS (Batandier et al. 2006), and DNA damage (Shown in Fig. 1) (Algire et al. 2012; Cabreiro et al. 2013) found that metformin extended the lifespan of Caenorhabditis elegans by changing microbial folate and methionine metabolism (Cabreiro et al. 2013). Metformin also has positive prevention and treatment effects on aging-related diseases. After continuous injection of metformin in SAMP8 mice for eight weeks, the expression of APPc99 and pTau in the mice brain was significantly reduced, and the learning and memory abilities of the mice were significantly improved (Farr et al. 2019). Ou et al. (2018) found that metformin exerted a neuroprotective effect on APP/PS1 mice via triggering

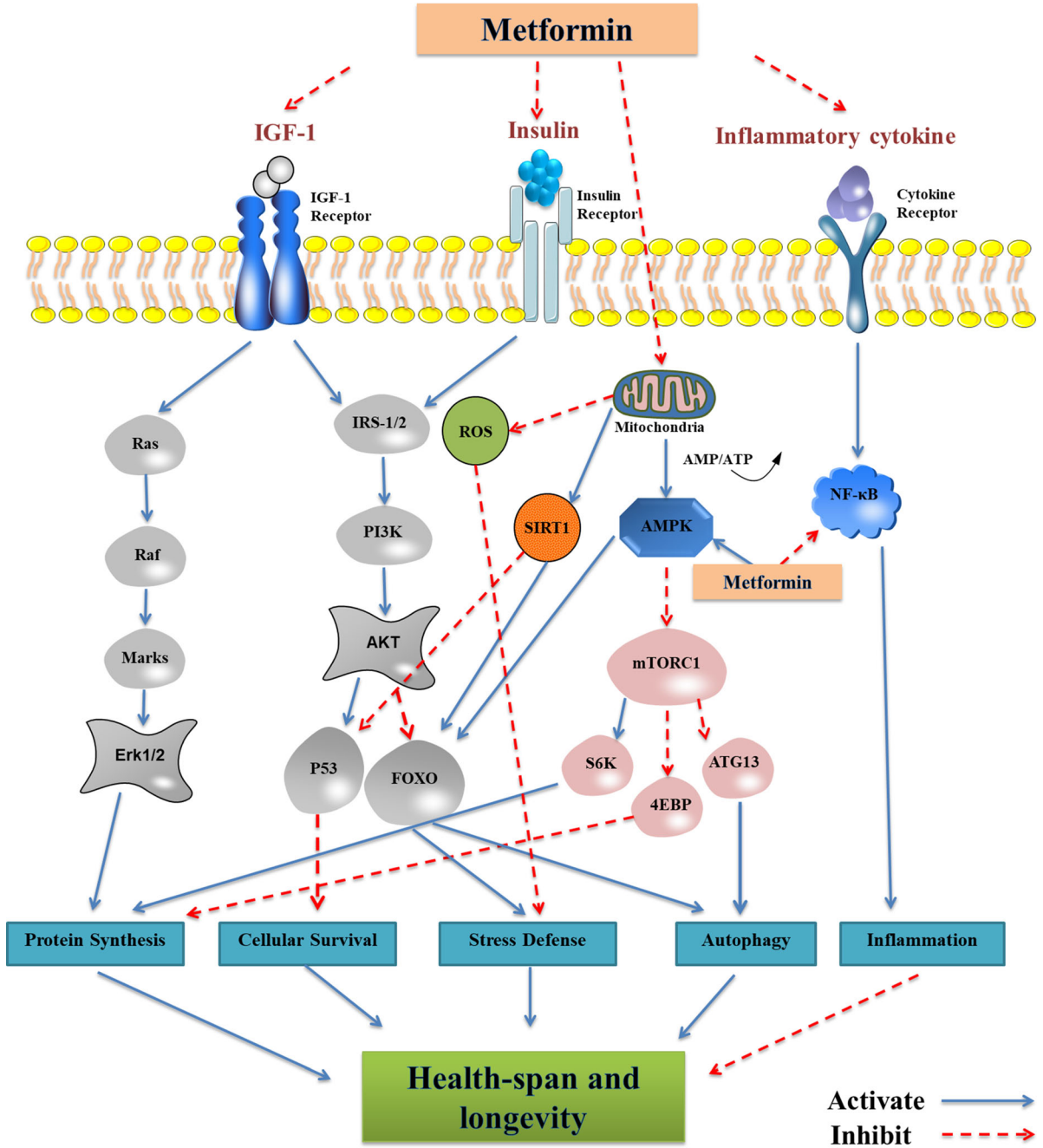

Fig. 1 Metformin targets the major pathways of aging. Extracellularly, metformin decreases insulin levels and IGF-1 signaling while influencing multiple cytokines to participate in anti-aging processes. Intracellularly, metformin reduces ROS production by inhibiting mitochondrial complex I in the electron transport chain generation and AMPK activation, simultaneous increase in mTOR signal inhibition and SIRT1 activation, which resulting in a longer life-span; Metformin affects inflammatory responses, cellular stress responses and autophagy responses, etc. by acting both inside and outside the cell. These cellular processes are the primary biological responses associated with aging

neurogenesis and anti-inflammation by regulating AMPK/mTOR/S6K/Bace1 and AMPK/P65 NF-κB signaling in the hippocampus (Ou et al. 2018). In addition, metformin inhibited SNCA phosphorylation and aggregation, reduced oxidative stress, and improved MPTP-induced motor and cognitive dysfunction in mice with PD (Lu et al. 2016; Patil et al. 2014). A survey of older adults with diabetes in Singapore also found that long-term treatment with metformin in patients with T2D may reduce the risk of dementia and cognitive impairment (Ng et al. 2014).

In addition to glucose homeostasis, the involvement of the tumor suppressor pathway is another target for metformin's action. A growing number of studies have shown that metformin has an inhibitory effect on some cancer cells in vivo and in vitro, such as rectal cancer and p53 mutant colon cancer (Algire et al. 2010; Buzzai et al. 2007; Gwinn et al. 2008; Hirsch et al. 2009; Hosono et al. 2010). In clinical trials, metformin also exerted excellent anti-cancer effects. A meta-analysis of diabetic patients treated with metformin and other drugs demonstrated a 30% lower incidence of cancers in metformin-allocated patients, such as breast cancer, gastric cancer, and prostate cancer (Col et al. 2012; Decensi et al. 2010; Tseng 2016). The survival rate was significantly improved for patients with pancreatic cancer who were treated with metformin (Li et al. 2017).

Although the therapeutic effect of metformin is well known for diabetes, there is evidence that long-term use of metformin may cause vitamin B12 deficiency in T2D patients and cause lactic acid accumulation in mice and humans (Aroda et al. 2016; Langan and Goodbred 2017; Marathe et al. 2017). In addition, the side effects of metformin also include irritation of the gastrointestinal tract, including diarrhea, nausea, flatulence, dyspepsia, vomiting, and abdominal discomfort, but in most cases, these symptoms are not obvious (McCreight et al. 2018). Stynen et al. (2018) reported that there are 745 proteins that are regulated by metformin treatment (Stynen et al. 2018). There is still uncertainty about whether these proteins demonstrate beneficial or potentially detrimental off-target effects when metformin is taken across the lifespan. Therefore, before providing metformin as a targeted aging drug, further research is needed to determine its broader effects, the molecular mechanism of action, and its safety implications.

Rapamycin

Rapamycin is a macrolide produced by Streptomyces hygroscopicus and was initially discovered as an antifungal agent. Recent studies have found that rapamycin can inhibit the mechanistic target of rapamycin (mTOR) protein kinase and extend the average lifespan of yeast, *C. elegans*, and fruit flies, but the role in mammals needs to be explored further (Johnson et al. 2013). Several other studies have shown that rapamycin could effectively extend the average and maximum lifespans of mice, such as C57BL/6, 129/SV, and UM-HET3 mice (Harrison et al. 2009; Anisimov et al. 2011; Chen et al. 2009; Neff et al. 2013). In addition, rapamycin has been found to inhibit tumorigenesis and extend the lifespan of many genetic early-onset models, such as p53 mutant mice, Apc mutant animals, Rb mutant mice, and HER-2/neu transgenic mice (Anisimov et al. 2010; Comas et al. 2012; Hasty et al. 2014). In addition, studies have found that rapamycin also has a neuroprotective effect. Oral rapamycin treatment could effectively improve cognitive function in elderly mice (Neff et al. 2013), reduce the pathological features of AD, and maintain the integrity of the blood-brain barrier by preventing neuronal loss and improving cognitive function (Carosi and Sargeant 2019). In addition to exhibiting excellent anti-aging effects in animal models, rapamycin has also shown unexpected results in clinical trials. A recent meta-analysis showed that rapamycin has a positive effect on tuberous sclerosis – a rare multisystem disease with the formation of benign tumors and neurological disorders (Sasongko et al. 2016). A clinical trial conducted by Chung et al. showed that topical treatment with rapamycin significantly increased $p16^{INKA4A}$ and collagen IV protein levels and improved the histological appearance of the subjects' skin tissues, which suggests that rapamycin can be used to some extent as an anti-aging therapy in human beings (Chung et al. 2019). The mechanisms of the effects of rapamycin on lifespan are shown in Fig. 2.

As an FDA-approved drug, rapamycin has been used in humans as a post-transplant immunosuppressant and for the treatment of renal cell carcinoma, coronary artery stent coating, lymphovascular smooth muscle tumor, and autoimmune diseases (McCormack et al. 2011). However, various and serious negative effects limit its use. As a typical mTOR inhibitor,

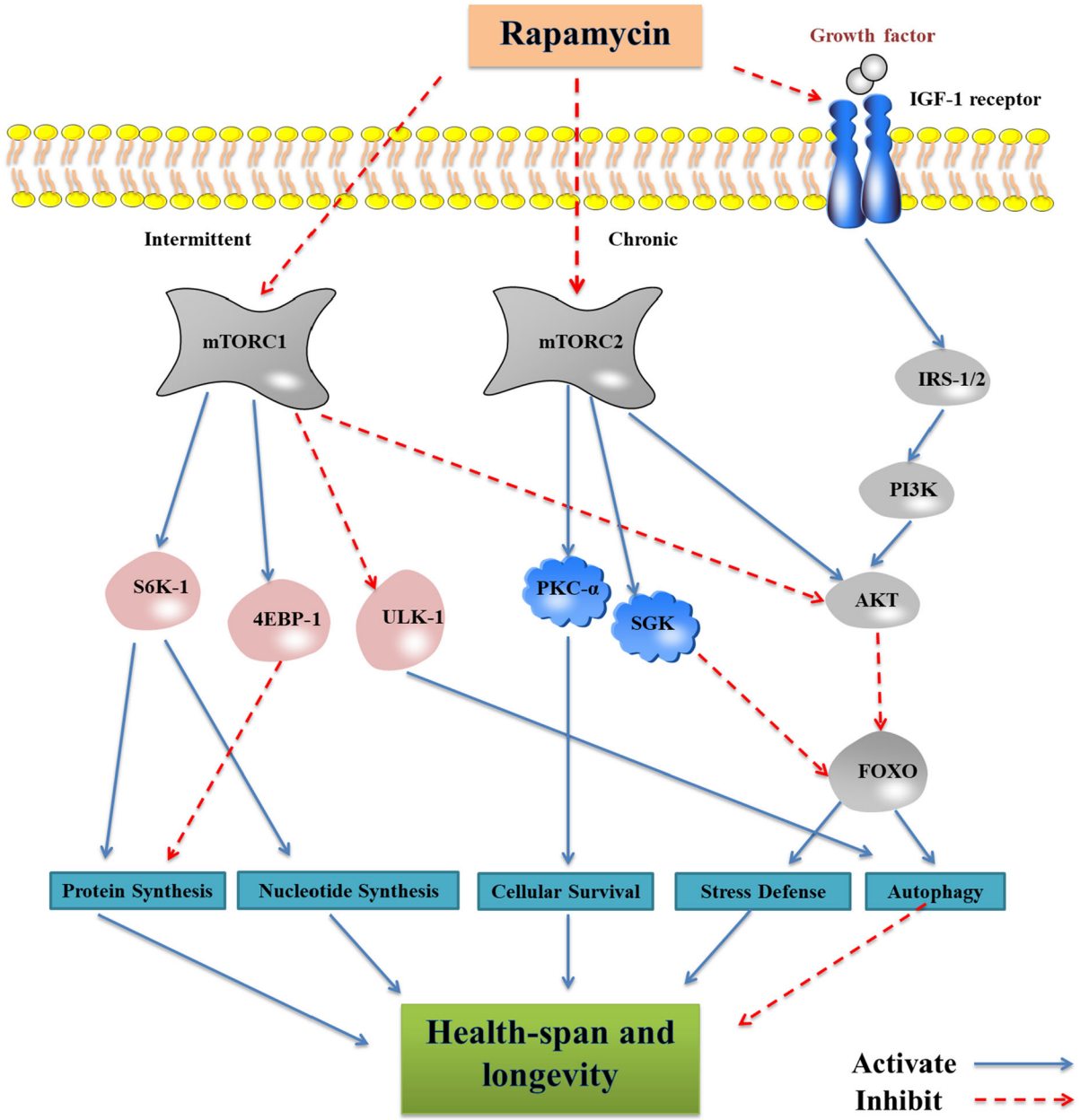

Fig. 2 Rapamycin regulates lifespan primarily through the mTOR signaling pathway. mTOR exists mainly in two functionally distinct complexes termed mTORC1 and mTORC2. Rapamycin inhibits mTORC1 on an intermittent basis, while long-term administration also inhibits mTORC2 in most tissues. Inhibition of mTORC1 promotes protein and nucleotide synthesis as well as autophagy responses, while also reducing cellular stress responses. These effects of rapamycin may promote longevity. In contrast, inhibition of mTORC2 leads to metabolic dysfunction and reduced lifespan, but the exact mechanism is unclear

rapamycin acutely inhibits mTORC1, which could promote longevity partially through the inhibition of S6K1, protein translation, and increased autophagy. Conversely, a long-term overdose of rapamycin will inhibit the expression of mTORC2, which can result in metabolic dysfunction and a decrease in the lifespan of male mice through an as yet undetermined mechanism (Arriola Apelo and Lamming 2016). Therefore,

further experiments are needed to determine the beneficial effects of rapamycin on mTORC1 inhibition-mediated aging and age-related diseases while minimizing the side effects associated with mTORC2.

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a phytoalexin found in many plant species, such as grapes, peanuts, and berries, which could respond to mechanical injury, fungal infection, and UV radiation (Silva et al. 2019). Resveratrol mainly promotes health and lifespan in yeast and *C. elegans* by activating the sirtuin family (Cao et al. 2018; Howitz et al. 2003; Price et al. 2012; Wood et al. 2004). Resveratrol can promote the viability and proliferation of human umbilical cord mesenchymal stem cells (hUC-MSCs) in a dose-response manner, mitigating senescence and inducing the expression of SIRT1, while inhibiting the expression of p53 and p16 (Wang et al. 2016). Although resveratrol has not been reported to extend the lifespan of wild-type mammals, studies have shown that resveratrol supplementation can extend the lifespan of mammals with impaired metabolism. Resveratrol can reverse the physiological indicators of mice on a high-calorie diet to reduce the risk of death by about 31% (Baur et al. 2006; Gocmez et al. 2016) suggested that resveratrol was effective in preventing a cognitive deficit in AD rats by inhibiting the production of inflammatory cytokines (Gocmez et al. 2016). Resveratrol combined with hUC-MSCs transplantation could improve the learning and memory functions of AD mice and enhance neurogenesis (Wang et al. 2018). In addition, resveratrol can pass through the blood-brain barrier and act on the brain of elderly patients with AD, prevent amyloid deposition, and reduce the formation of plaque (Sawda et al. 2017) Zhang et al. (2018) showed that resveratrol alleviated motor and cognitive deficits in PD model mice in a dose-dependent manner (Zhang et al. 2018). Emerging studies have shown that resveratrol can significantly reduce overall tumor development by promoting apoptosis, regulating the cell cycle, and inhibiting Cyclooxygenase (COX) activity and prostaglandin production (Kalra et al. 2008). Resveratrol has also been found to mediate the protective effects against inflammatory diseases and cardiovascular diseases through various mechanisms (Park et al. 2012; Tsai et al. 2014; Xia et al. 2017; Zhu et al. 2018). The mechanisms of the effects of resveratrol on lifespan are shown in Fig. 3.

Resveratrol has shown great promise in multiple animal models. However, its role in human clinical trials is still controversial. A 26-week intervention trial performed with 23 overweight elderly patients concluded that resveratrol supplementation might improve glucose metabolism, hippocampal functional connectivity, and memory function (Witte et al. 2014). But a recent meta-analysis showed the opposite result. A follow-up study on 225 patients showed that resveratrol did not have a positive effect on memory and cognition (Farzaei et al. 2018). In addition, Gliemann et al. (2013) showed that resveratrol supplementation reduced the positive effect of exercise training on blood pressure, blood cholesterol, and maximal oxygen uptake but did not affect the retardation of atherosclerosis (Gliemann et al. 2013). This phenomenon implies trying not to consume foods containing resveratrol during exercise. Resveratrol has been tolerated in animal experiments, but when administered in high doses, resveratrol may cause serious side effects such as diarrhea and local allergies (la Porte et al. 2010; Popat et al. 2013). In addition, resveratrol has a low bioavailability, which may limit its clinical application. A further challenge is that resveratrol is difficult to use in large-scale clinical trials at this stage.

Senolytics

Senolytics, drugs that selectively clear senescent cells, have been developed recently and may be a novel strategy for extending the healthspan and lifespan. Senescent cells increase several anti-apoptotic regulators, including dependence receptors, PI3K/Akt and BCL-2, which can jointly regulate the ability of cells to resist apoptosis (Zhu et al. 2015). Dasatinib (D) and quercetin (Q) could induce apoptosis in senescent fat progenitor cells and alleviate several aging-related phenotypes in premature aging and natural aging mice induced by injury (Zhu et al. 2015). Navitoclax, a BCL-2 family inhibitor, could reduce the viability of senescent human umbilical vein epithelial cells (HUVEC) and IMR90, but it has no effects on human primary preadipocytes (Zhu et al. 2016). Other senolytics, such as ABT-737, A1331852 and A1155463 can also inhibit BCL-2 (Zhu et al. 2017) and clear senescent cells. Navitoclax could remove

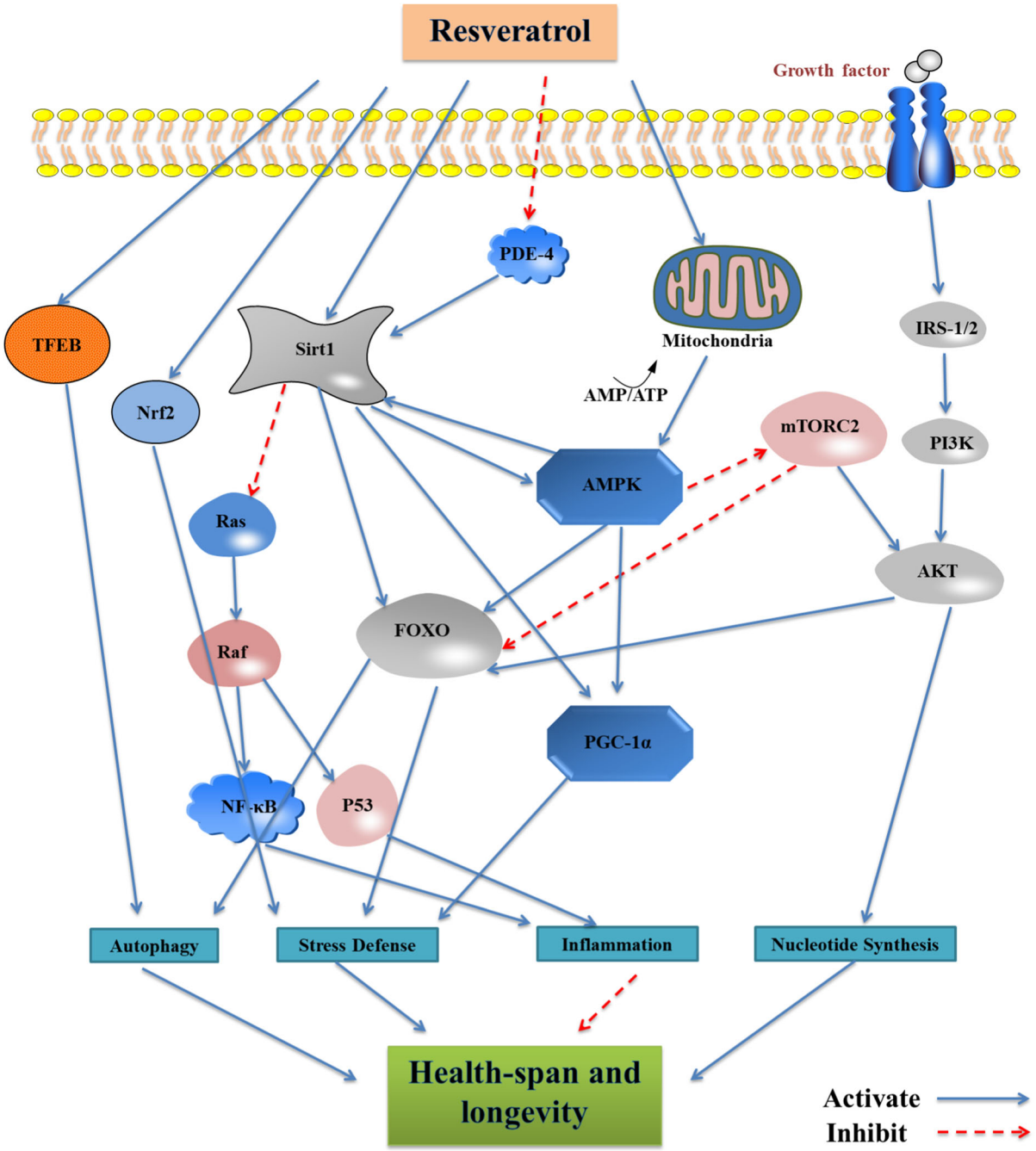

Fig. 3 Resveratrol is involved in anti-aging as an activator of the sirtuin family and the Nrf2 pathway. Inhibition of mitochondrial ATP production by resveratrol leads to activation of AMPK, which enhances NAD + availability thereby overcoming the rate limitation imposed by this cofactor on SIRT1 enzyme activity. In turn, resveratrol directly activates SIRT1 thereby positively controlling AMPK activity. Together, AMPK and SIRT1 form a positive feedback pathway to prolong life by modulating multiple downstream factors. In addition, resveratrol can act directly on transcriptional regulators thus acting as an anti-inflammatory and antioxidant effect

SASP-targeted senescent cells (SNC) during the formation of atherosclerosis (Childs et al. 2016) and prevent hematopoietic SNC from rejuvenating (Chang et al. 2016). ATB263 clears a series of senescent cancer cells and eliminates chemotherapy-induced senescent cells, reducing cancer relapse and metastasis in mouse models (Demaria et al. 2017; Wang et al. 2017). Senolytic (D + Q) treatment reduced the abundance of senescent cells in the brains of obese mice, restored neurogenesis, and reduced neuropsychiatric dysfunction (Musi et al. 2018; Ogrodnik et al. 2019; Zhang et al. 2019). In addition, senolytics may be effective for a variety of age-related diseases, such as idiopathic pulmonary fibrosis, sarcopenia, osteoarthritis, and glomerulosclerosis (Kim and Kim 2019). As research has progressed, senolytics have also shown promising results in clinical trials. Cox et al. (2015) conducted acute and chronic interventions using curcumin to treat elderly patients respectively and showed that both treatment regimens significantly improved their learning and memory abilities (Cox et al. 2015). Justice et al. (2019) found that senolytics (D + Q) significantly improved the clinical performance of 14 patients with idiopathic pulmonary fibrosis (IPF) (Justice et al. 2019). It can also effectively eliminate p16 INK4a-positive cells, reduce SA-β-gal activity, and decrease the release of inflammatory factors in diabetic nephropathy (Hickson et al. 2019; Rossman et al. 2018).

Although senolytic therapy exhibits exciting anti-aging effects, the current understanding of senolytics has its own limitations. Navitoclax has been reported to cause severe thrombocytopenia and neutropenia, and these side effects limit its application (Niedernhofer and Robbins 2018). Another potential problem is tissue atrophy, which is caused by senescent cells being largely eliminated. In addition, senolytics eliminate not only the harmful effects of senescent cells but also their beneficial effects. Although cellular senescence is the cause of aging and aging-related diseases, senescent cells can also play a positive role. For example, senescence is an effective barrier against tumorigenesis in the early stages of cancer (Calcinotto et al. 2019). Therefore, the dual biological function of senolytics must be evaluated. Furthermore, it is necessary to advance the current version of senolytics by improving its targeting capability and selectively inhibiting its harmful effects on cells and tissues. Precise clinical trials of senolytics therapy have not yet been performed. More translational studies should also be considered.

Caloric restriction

Recently, progressively more research has recommended caloric restriction (CR) to reduce obesity-induced aging-related diseases (Salvestrini et al. 2019). The aim of CR is to reduce calorie intake without malnutrition and to improve the viability of organisms (Broskey et al. 2019). An accumulating number of studies have reported that CR has a positive effect on DNA repair and telomere mechanisms. The incidence of tumors in TERT transgenic (TgTERT) mice was significantly reduced with CR, which also prolonged their lifespan compared to wild-type (WT) controls under the same diet (Vera et al. 2013). Reducing calorie intake can increase metabolic efficiency and prevent cell damage (Picca et al. 2017). It can also extend the lifespan of rodents and humans by reducing insulin, glucose, and the IGF-1 signaling pathway (Hwangbo et al. 2020; Pifferi and Aujard 2019a). In mammals, it is clear that CR induces the expression and activity of sirtuins in many tissues, which are closely related to aging (Imai and Guarente 2010). The positive effects of CR on inflammation and insulin resistance have been demonstrated in a rat model of age-associated inflammation by regulating GSH redox status and NF-κB, SIRT1, and FoxOs (Chung et al. 2011; Horrillo et al. 2011). Important improvements were shown in the onset and development of CVD and diabetes. The incidence of CVD is reduced with CR by controlling the mechanisms of maintaining cardiac activity, such as autophagy, proteasome-mediated turnover, apoptosis, and mitochondrial quality, to control its effects during aging (Rattan 2014). PGC-1α expression and mitochondrial biogenesis stimulated by AMPK and SIRT1 in muscle have been associated with the reduction of insulin resistance, and the use of CR or CR mimickers, such as resveratrol or metformin, contribute to preventing the onset and the progression of the diseases (Gerhart-Hines et al. 2007). Human clinical trials have also demonstrated positive effects of CR (Lorenzini 2014). A survey by Most et al. (2018) showed that continuous CR in healthy, nonobese individuals could reduce the incidence of cardiovascular disease by 30% (Most et al. 2018). Redman and Simin found that long-term CR without malnutrition could enhance the efficiency

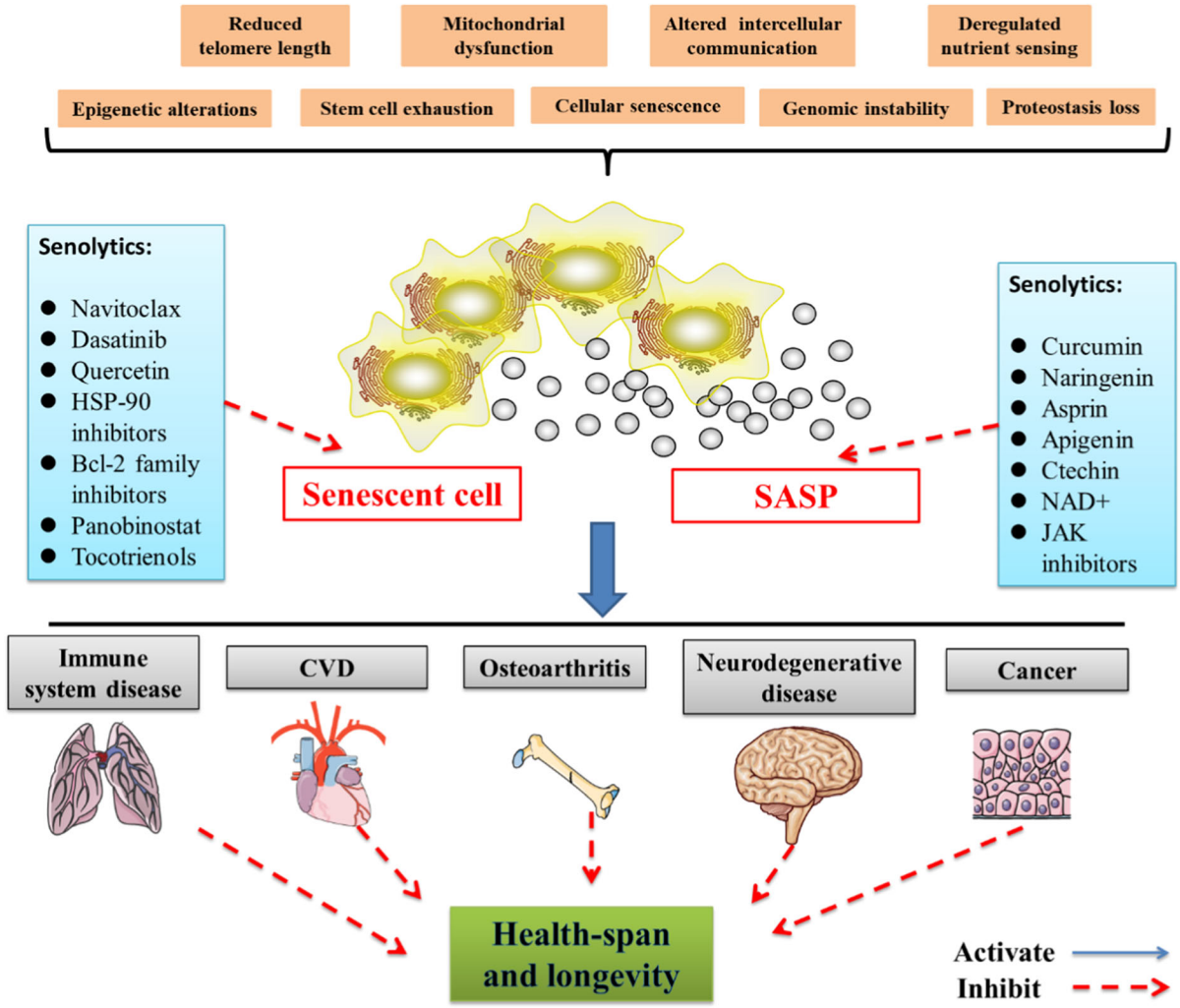

Fig. 4 Senolytic therapies target aging. During the aging process, senescent cells accumulate in large amounts in tissues and are associated with the development of various age-related diseases. Senolytics can help slow down the aging process by eliminating the accumulation of senescent cells, reducing age-related diseases and prolonging healthspan. Uncontrolled activation of SASP can cause chronic inflammation, leading to tissue dysfunction, this ultimately leads to aging and age-related diseases. Senolytics also can positively impact aging-related diseases by modulating the regulatory network of SASP in senescent cells and by inhibiting SASP from exerting its deleterious effects

of resting energy expenditure, thereby reducing oxidative damage to tissues and organs (Redman et al. 2018), and inducing significant suppression of inflammation, as shown by a two-year CR dietary intervention (Meydani et al. 2016).

Despite the positive effects of moderate CR on human aging, some of the possible negative effects of CR should also be considered. As people get older, physiological reserves diminish, leading to reduced resistance to various stressors. In the case of malnutrition, these adverse factors can be magnified-a problem that faces many older people. Therefore, CR should not be used as a potential intervention for treating diseases in this specific population (Pifferi and Aujard 2019b). Also, people with a low body mass index (BMI, less than 21 kg/m^2) should also be cautious of utilizing CR, as this could lead to rapid weight loss and thus increase the risk of further health problems (Le Bourg and Redman 2018). In addition, a study by McGrath et al. found that exercise could cause bone loss and appeared to be harmful to the bones of mice in the CR group compared to the control

group (McGrath et al. 2020). Clinical studies have also found that CR could decrease bone mineral density as well as increase the risk of osteoporotic fractures compared to a control group (Villareal et al. 2016). Therefore, before engaging in CR as a therapy to slow down the aging process, many factors, such as the patient's physical condition, mental state, and BMI, should be taken into consideration. Blindly engaging in dieting or CR should not be promoted (Fig. 4).

Conclusions

Medicine has undergone a gradual shift in its underlying concept, from "sick care" to "health care".That is to say, medicine is moving away from focusing on treatments after the occurrence of a disease towards intervening before the recognized risk factors progress to disease onset. Defining the hallmarks of aging helps to establish a framework of aging-related mechanisms and thus provides theoretical support for improving human health and extending the lifespan. Due to the continuously growing trend of an aging population, the anti-aging strategy is undoubtedly an increasingly important area for the pharmaceutical industry and public health organizations. However, considering the limitations and side effects of anti-aging drugs, there are presently too many concerns that need further clarification. Therefore, collaborative efforts from multidisciplinary researchers are required to advance these potential treatment strategies.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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