Addressing the Fever Dream of Curing Aging: a Comprehensive Review on the Phenomena of Biological Aging

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Aging is characterized by declining regenerative capacity, telomere attrition, chronic low-grade inflammation and accumulation of senescent cells. Senescent cells can promote aging via acquisition of a senescence-associated secretory phenotype (SASP) that produces pro-inflammatory cytokines and promotes tissue inflammation. Chronic inflammation and oxidative stress go hand-in-hand with accelerated telomere attrition and increased replicative senescence in the approaching Hayflick limit. Multiple interventions have been suggested to slow down these interlinked processes; such interventions involve enhancement of cellular clearance (autophagy) as well as genetic manipulation of the regulators including telomerase components or nutrient-sensing pathways. CRISPR-Cas9 is an example of such a technique; this technology allows performing precise DNA modifications, which can either increase or decrease the expression of certain genes involved in senescence, inflammation, telomere maintenance or autophagy. This review aims at illustrating how major aging mechanisms interrelate as an integrated network of processes.

Introduction

Aging is an inevitable biological process of progressive loss of physiological resilience and functional capacity[1]. Chronological age refers to the age of individual measured by time lived, while biological age describes the cumulative molecular and cellular changes, which make the individual susceptible to dysfunction and disease[2]. Aging might be experienced as wrinkles or joint pain, but at a cellular level, aging can be characterized by markers including telomere shortening, genome instability, mitochondrial dysfunction, altered metabolism, impaired proteostasis, and senescence[3]. Importantly, the above mentioned hallmarks do not occur independently; instead, they interact as a part of an interconnected network of processes[4].

Increasing mean life expectancy makes the burden of age-related chronic diseases a growing concern, which calls for a distinction between life extension and health span – years spent without disease[5]. Much of the information about aging mechanisms was discovered on the model organisms such as mice and C. elegans, where various treatments and genetic manipulations were examined throughout the whole lifespan[6]. In this regard, current interest in slowing down the aging process is mainly focused on the interventions, which can alter the conserved mechanisms including increased autophagic flux and modulations of telomere maintenance and nutrient sensing regulators such as Rubicon and mTOR pathway[7]. This review will describe how telomeric attrition, cellular senescence, autophagy and CRISPR-Cas9-based interventions fit into an interconnected framework of aging and anti-aging[8].

Methods

Literature search for this narrative review was conducted using keywords “aging”, “telomere”, “cellular senescence”, “SASP”, “autophagy”, “mitophagy”, “mTOR”, “rapamycin” and “CRISPR” on PubMed and Google Scholar. Only peer-reviewed articles were included in the review. Primary experimental studies were preferentially included; however, several landmark review papers were included when they provided relevant conceptual frameworks. The strength of evidence for the key points is presented in accordance with the study context (in vitro studies, animal studies, and human studies), while any associations are stated only in the case when the causality was not proved. The study quality is determined qualitatively according to the study design, appropriateness of controls and relevance to the aging.

A PRISMA-style flow diagram showing the screening process for the subset of the articles is provided in Figure S1.

Biological Aging

Biological aging is related to various micro- and macroscopic mechanisms, which contribute to accumulation of cellular senescence and can be observed in processes such as telomere attrition and mitochondrial dysfunction. Hallmarks of biological aging cannot be considered independently since they

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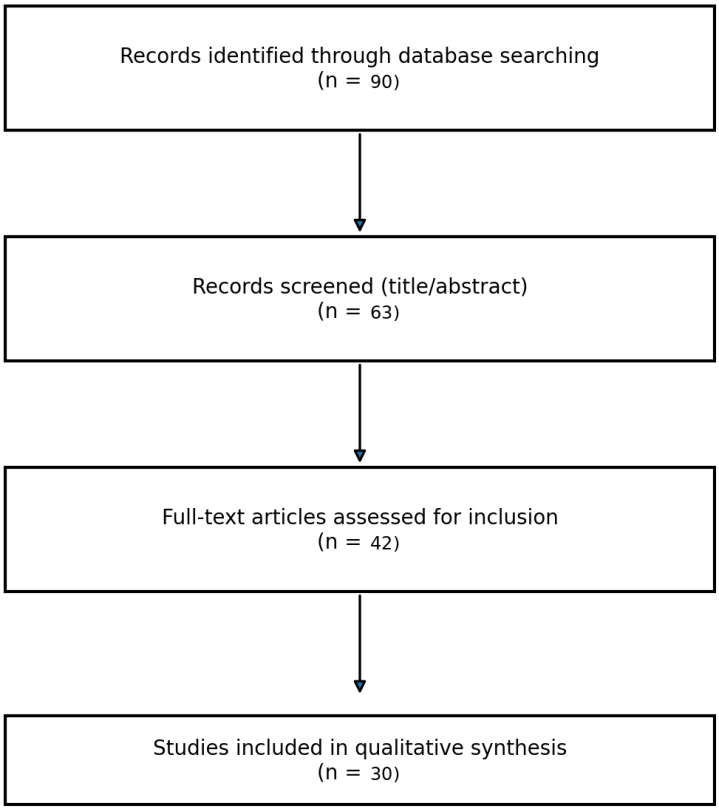

Figure S1. PRISMA-style flow diagram summarizing screening for the studies directly cited in this review.

comprise a network with the mutual interactions and causality[9]. First, there is genomic instability – accumulation of DNA damage caused by endogenous factors (errors in replication, mutations) and external stressors (radiation, toxins)[10]. Damage to the genome can contribute to telomere attrition and other hallmarks[11].

It is important to distinguish global genomic instability from the telomeric DNA damage. Genomic instability describes lesions throughout the genome, whereas telomeric damage describes damages that occurred in the repetitive, guanine-rich chromosome ends. Such damages cannot be easily repaired because of their location, and the persistent DNA damage signal can persist despite repairs in other parts of genome[12]. Since telomere repeats are guanine-rich and the telomere is repeatedly replicated, inflammation and mitochondrial ROS can have damaging effect on the telomere repeats, linking mitochondrial dysfunction to increased telomere shortening[1].

Shortening of telomeres contributes to aging, because critically short telomeres can induce DNA damage response leading to replicative senescence and cell cycle arrest as dividing cells reach their Hayflick limit[2]. Accumulation of senescent cells causes a reduction in the ability of tissues to regenerate, causing slower healing[3]. Dysfunctional telomeres cause an increase in inflammatory responses, and this reinforces the cycle of senescence and inflammation[4]. Genomic instability, for example, is one cause of telomere loss that can be worsened by mitochondrial dysfunction. Dysfunctional mitochondria increase the levels of ROS and initiate inflammatory signaling (NF-κB activation), which leads to increased senescence and inflammation[5]. ROS contribute to telomeric DNA damage; therefore, mitochondrial dysfunction exacerbates the problems with telomere attrition, contributing to feedback loop and biological aging[6].

Cellular Senescence

Cellular senescence is a condition of irreversible cell cycle arrest induced by replicative exhaustion (typically associated

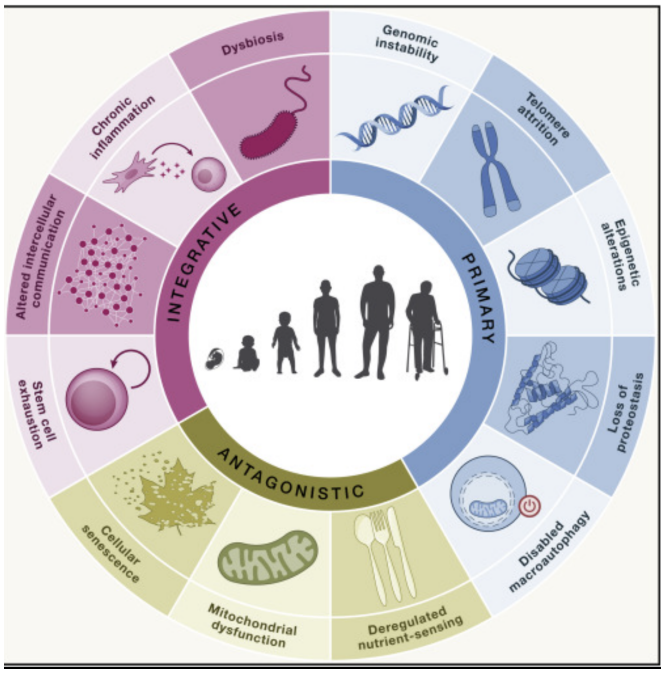

Figure 1. Framework for the hallmark of aging in studies of health and longevity. This framework demonstrates different aging processes that include cellular senescence, dysfunctional mitochondria, and shortened telomeres. Adapted from [1].

with telomere shortening) or stress-induced damage (oxidative, genotoxic and oncogenic stress) [13]. Senescence is due to multiple causes, as shown in Figure 1. Senescence acts at first as a tumor suppressor by making sure that the damaged cells do not divide (Figure 1) [14]. There are three main types of cellular senescence, namely replicative senescence, stress-induced senescence, and oncogene-induced senescence. While these different types have different triggers, they all end up with the ability to arrest cell cycles and produce SASP [15].

In the context of aging, senescence can be induced by chronic oxidative stress and telomere dysfunction rather than over-proliferation of cells [16]. Cellular senescence acts as a double-edged process in this regard because while it prevents tumorigenesis through inhibition of proliferation of the damaged cells, senescent cells impair regenerative potential and contribute to age-related dysfunction [7]. Harmful consequences of cellular senescence for the organism are tightly related to signaling pathways of DNA damage response. For instance, DNA damage may lead to activation of p53-p21 and p16-Rb pathways causing cell cycle arrest [13]. In the long term, most of the senescent cells acquire a senescence-associated secretory phenotype (SASP), which is represented by release of pro-inflammatory cytokines (IL-6, IL-8) [14]. The higher level of chronic inflammation is associated with aging [15]. It means that the senescence leads to the inflammation, which reinforces telomere dysfunction and further senescence [16].

Telomeres

DNA damage can induce rapid shortening of telomere length and lead to the loss of replicative capacity of dividing cells [8]. Telomere dysfunction contributes to the development of age-related diseases and is a crucial factor of biological aging [9]. The length of the telomere determines the maximum number of cell divisions, and telomeres that are shorter result in reduced regenerative ability [10]. Even though the shortening of the telomere is one of the factors responsible for aging, it is an inevitable process of cell division [11]. The telomeres are repeating units of DNA found at the ends of chromosomes and act as a buffer for coding DNA losses during replication [12]. Due to the so-called end-replication problem, telomeres shorten after every round of cell division in most somatic cells, and the mean telomere length becomes an indicator of replicative history and in some cases biological age [5]. Shortening of telomeres to the critical level can cause cell senescence and limit cell division [6].

When telomeres shorten to the critical level, dividing cells reach the replicative limit (Hayflick limit) at which the dys-

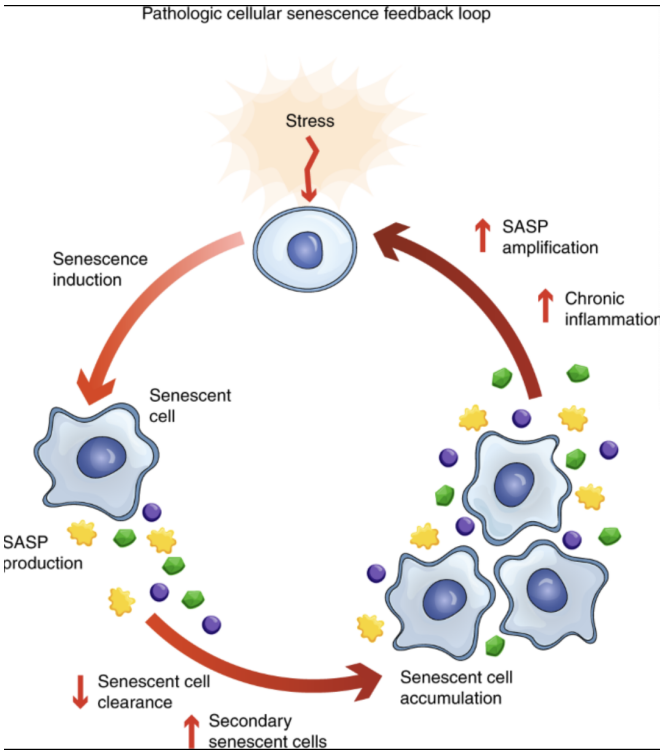

Figure 2. Senescence-accelerated senescence-associated secretory phenotype (SASP). This figure illustrates how cellular damage and senescence can increase SASP and inflammation, which consequently lead to tissue damage and increased cellular senescence. Adapted from [13,14].

function of telomeres activates persistent DNA damage signaling and cell cycle arrest. Cells either become subject to replicative senescence or apoptosis, depending on the context[8]. Inflammation plays an important role in inducing oxidative stress and increases ROS concentration, thereby increasing the rate of telomere shortening and stimulating senescence-related inflammation[9]. It is clear how inflammation and telomeres dysfunction influence each other, creating a cycle shown in Figure 2.

Autophagic Flux

Given the strong relationship between chronic inflammation in aged tissues and biological aging, interventions that reduce inflammatory burden can be considered as possible methods for disrupting the feedback loops leading to the telomere attrition[17]. Among molecular mechanisms attracting much attention there is autophagy[18]. Autophagy is a cellular recycling pathway, which is essential for the maintenance of cellular homeostasis and involves sequestration of the cytoplasmic content (proteins and organelles) in the double-membrane autophagosomes and subsequent degradation by lysosomes[19]. Generally, autophagy is stimulated by nutrient depletion and cellular stressors, which inhibit mTORC1 and/or activate energy sensing pathways leading to activation of ULK1 complex and formation of autophagosomes[20]. In this way, cells can recycle the amino acids and lipids to maintain metabolism during the stress or starvation[21].

Autophagy is involved in maintaining the mitochondrial quality via removal of the damaged mitochondria by means of mitophagy[22]. Elevated autophagic flux in various experimental models was shown to lead to reduced aging-associated pathology and maintenance of cellular homeostasis[23]. Elevated autophagic flux may prevent accumulation of the malfunctioning mitochondria resulting in reduced ROS generation and inflammatory signaling that cause chronic inflammation[17]. During mitophagy, the damaged mitochondria are tagged and isolated in autophagosomes that later fuse with lysosomes for degradation[18]. In such a way, malfunctioning organelles are eliminated before inflammatory signaling begins[19]. Increased autophagic flux may reduce the accumulation of dysfunctional organelles and hence the generation of ROS and inflammatory signaling caused by the dysfunctional mitochondria[19].

The lower level of inflammatory and oxidative stress correlates with mechanisms of slowing down the telomere attrition (Figure 3)[20]. However, there are multiple reports about age-associated reduction of autophagy efficiency, causing accumulation of misfolded proteins and dysfunctional organelles and exacerbation of cellular stress[21].

Autophagy in Healthy Aging

To prevent the contribution of the oxidative stress to aging, maintenance of the autophagic flux is often suggested as a method[24]. As autophagy maintains the cellular homeostasis, the role of autophagy in preventing accumulation of dysfunctional cells and organelles is relevant to the healthy aging[25]. One of the age-associated changes is the increased expression of Rubicon, which is a negative regulator of autophagy, inhibiting the process of autophagosome-lysosome fusion (Figure 4)[18]. In animal models, the decreased expression of Rubicon increases the autophagic activity, indicating the improved clearance in older tissues[18]. Therefore, the promotion of the healthy aging would include downregulation of Rubicon and processes, which increase the autophagic flux, rather than opposite[18].

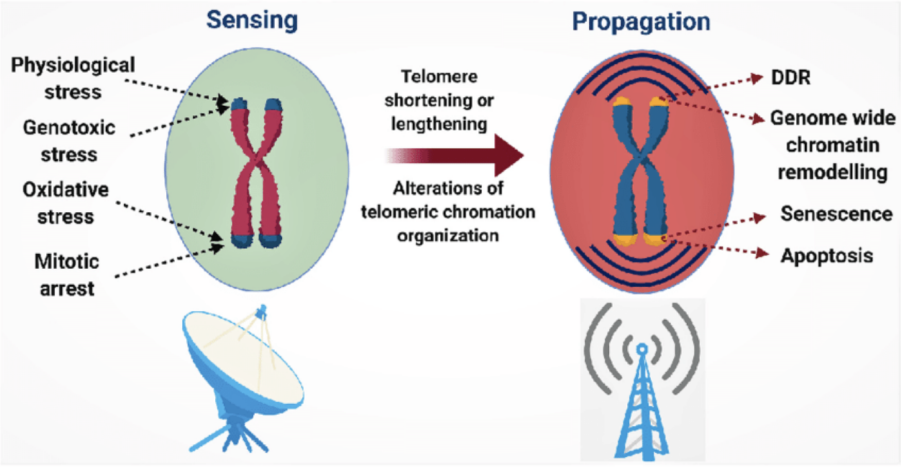

Figure 3. Roles of telomeres in detecting and communicating stresses. This figure shows how oxidative, replicative, and genotoxic stresses trigger telomere damage and chronic DNA damage response, thus causing senescence and dysfunction. Adapted from [10,11].

Several approaches are explored to oppose the age-associated decline of autophagy. Caloric restriction and fasting paradigm can increase the autophagic markers in multiple model organisms; however, protocols and reversibility of the treatment depend on the particular model and experimental design[24]. Mechanistically, nutrient deprivation decreases the activity of mTORC1 and increases the autophagosome formation; it allows maintaining the metabolism by recycling the organelles[25]. The increased autophagic flux can enhance clearance of dysfunctional mitochondria, reducing the levels of ROS and inflammatory signaling and thus decreasing telomere attrition; however, the evidence about the changes in telomerase activity is context-dependent and limited by the human studies[26].

It has been shown that increased levels of autophagy are associated with longer lifespan and decreased formation of protein aggregates, and rapamycin increases the lifespan of mice by influencing nutritional and autophagy pathways[27]. An increase in autophagic activity is beneficial in protein aggregation and removal of dysfunctional organelles, thus decreasing the cellular burden[22]. Autophagy also contributes to the stem cell function, immune regulation and metabolic flexibility, which are relevant to the healthy aging[23]. However, the autophagic capacity tends to decline with age because of autophagy inhibitors such as Rubicon and sustained activity of mTORC1, which limit autophagosome maturation and lysosomal clearance[28]. Rapamycin (sirolimus) inhibits mTORC1 and releases the autophagy-related repressive effect in animal models[17].

Rapamycin and mTOR

Autophagic flux decreases with increasing age, partly owing to the increase in expression levels of Rubicon and continuous activation of mTORC1, as seen in Figure 4 (Figure 4)[18,25]. Mechanistic target of rapamycin (mTOR), especially the mTORC1 complex, acts as an important inhibitor of autophagy in the presence of ample nutrients[25]. The activation of mTORC1 blocks the ULK1 initiation complex, composed of ATG13, hence preventing the gene expression necessary for the development of autophagosomes and lysosomes[24].

A decrease in autophagic flux results in the accumulation of dysfunctional organelles and protein aggregates in the cells[26]. In experimental systems, the impaired autophagy is associated with the increase in senescent cells burden and inflammation, confirming the ability of autophagy to limit the SASP-driven inflammation[27].

Pharmacologically, rapamycin (sirolimus) inhibits mTORC1 and increases the autophagy-related activity in model systems[29]. Reducing the mTORC1-mediated repression of ULK1 and biogenesis programs of lysosomes (TFEB-regulated pathways), rapamycin can release the repression of autophagy, increasing degradative clearance and stress resistance[28]. In mice, the treatment with rapamycin in later life extends the lifespan, confirming its role as an intervention for aging in vivo[26].

Despite the fact that the telomere shortening and decreased telomerase activity are the common indicators of biological aging, interventions aimed at the telomere integrity and regulation of telomerase have been developed in the experimental models; these interventions require careful evaluation of the tissue specificity and tradeoffs, including the risk of cancer[25].

Gene Editing in Healthy Aging

Telomere erosion and shortening are some of the major features of aging[30]. For proliferative cells, having long telomeres delays the appearance of replicative senescence caused by short telomeres[31]. There are various methods of gene therapy that have been developed with an objective of regulating the activity of telomerase or maintaining telomeres in order to prevent replicative senescence; but these benefits come with conditions and need to be evaluated on a case-by-case basis[32].

Among the gene therapy interventions there are those which target the telomerase. In the mouse models, telomerase gene therapy or telomerase activation can restore the telomere length and improve the tissue function in certain conditions, but the translation to human remains questionable and needs safety evaluation[33]. At the molecular level, the activity

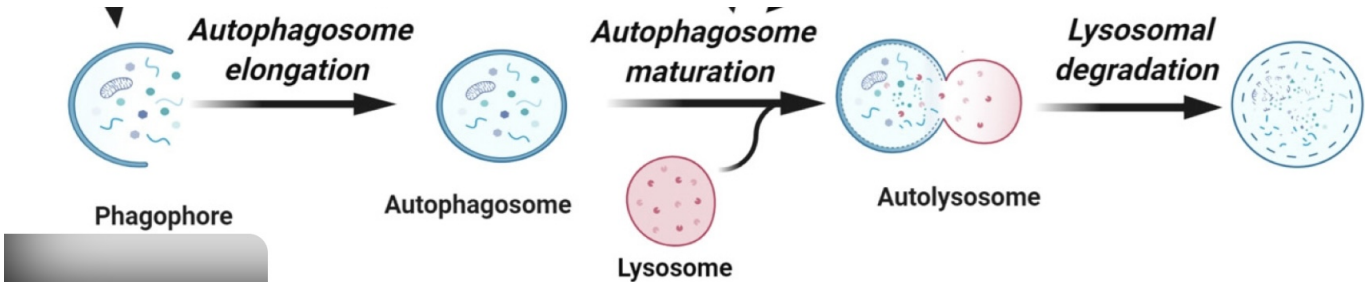

Figure 4. Inhibition of autophagy by mTORC1. This figure represents the effect of mTORC1 inhibition on different stages of autophagosome generation and lysosomes formation due to rich nutrients. Adapted from[25].

of telomerase is determined by both catalytic subunit (TERT) and RNA template (TERC); the interventions targeting these components and their regulation can be performed[34].

The gene modulation can also target other aging pathways such as nutrient sensing (mTOR) or autophagy regulators; these pathways are interconnected with inflammation and senescence[35]. One of the tools for such targeted modulation is CRISPR-Cas9, which enables the programmable gene editing[36].

CRISPR-Cas9 Editing in Mitigating Telomeric Attrition

CRISPR-Cas9 editing is a versatile tool for targeted genome editing, which can be used for disruption, correction or regulation of the genes implicated in aging-related pathways[30]. It uses guide RNA for directing Cas9 enzyme to the specific sequence, introducing double-stranded break, which can be subsequently repaired to produce the targeted edit[31]. In theory, CRISPR technology can be used to target senescence regulators, telomeres, and autophagy; however, using this technology to treat aging requires that certain factors be considered, including delivery, off-target effects, mosaicism, and safety[32].

The CRISPR technique is responsible for facilitating gene deletion and also up-regulating the expression of genes through CRISPR transcriptional activation[32]. In telomeres, this type of technology can increase the activity of telomerase by enhancing the expression of the TERT protein. TERT and telomerase RNA component (TERC) cooperate in adding TTAGGG repeats to telomeres, compensating the end-replication problem and maintaining the telomere length[30]. Theoretically, the continued presence of telomerase activity could prevent replicative senescence in cells that are continually dividing; but this poses certain problems concerning specificity and the potential for inducing cancer[31].

Maintenance of telomere length allows cells to divide several more times before attaining a replicative endpoint that is typically associated with critically short telomeres[32]. In principle, it can help to maintain the regenerative capacity of proliferative tissues; however, any intervention, which increases replicative capacity, must be evaluated for oncogenic risk and tissue specificity[35].

Telomerase

Telomerase plays an important role in the preservation of telomere lengths in germline cells, stem cells, and a number of cancerous cells; telomerase also serves to reduce the telomere erosion to some extent in several somatic cells[33]. One of the main reasons behind telomere erosion is the so-called end-replication problem, which means that DNA polymerase cannot copy the ends of linear chromosomes, thus causing the continuous loss of the sequence during each round of replication[34]. The action of telomerase, mostly via its catalytic component TERT, involves adding TTAGGG sequences to the chromosome ends based on RNA template (TERC)[36].

Since telomerase functions in maintaining cell replicative potential, its constant activation in somatic cells is likely to increase chances for the development of cancer, especially when tumor-suppressor checkpoints are compromised. Therefore, telomerase targeting interventions are always discussed in a tissue-specific way and are evaluated together with cancer risk[12]. Telomerase is often referred to as telomere integrity maintainer because of the fact that maintaining the telomere length reduces the persistent telomere-associated DNA damage signaling, which leads to senescence[33]. If the telomeres are damaged or shortened to the critically reduced level, activation of the DNA damage response occurs in this case, where persistent signaling at telomeres increases inflammatory and senescence phenotypes[34]. Besides being involved in the regulation of telomere length, TERT seems to have other functions, including the effect on mitochondria by reducing the production of reactive oxygen species and maintaining the stability of mtDNA. The magnitude of this involvement and relevance to human aging is still unclear[36].

Summary of Interventions and Evidence

Table 1 is the summary of main interventions mentioned in this review, their targets, the context of evidence, and limitations.

Conclusions

Aging is an inevitable biological process that cannot be prevented, although some interventions might delay this process[2]. Thinking about aging as an integrated system allows identifying possible disruptions to feedback loops[15]. The interventions mentioned above comprise pharmacological targeting of mTOR using rapamycin to boost autophagy and various genetic interventions to promote telomere integrity and senescence[22]. Altogether, they are aimed at reduction of inflammatory stress and cellular damages to slow down telomere erosion[1].

Future Directions

While rapamycin is considered one of the most promising candidates for anti-aging interventions in animal models, the therapeutic value of the compound in humans has not been evaluated yet[26]. The fact is that rapamycin (also known as sirolimus) is used in clinical practice as an immunosuppressive drug during organ transplantations; however, whether there are advantages or disadvantages of using it as an anti-aging compound is still unknown[29]. As a result, in the future, translational studies can use new methods like bioprint-

Table 1 Summary of interventions, evidence base, and limitations discussed in this review.

Intervention	Primary target/pathway	Evidence base	Main reported outcome(s) in cited studies	Key limitations/risks	Key reference(s)
Caloric Restriction and Fasting Regimens	Inhibition of mTORC1; ULK1 activation; autophagosome formation	Mostly from animal models and human studies	Increase of autophagy-related processes and increased resistance to stress in animal models	Protocol-specific; translatability to humans is unclear	16
Rubicon downregulation	Alleviation of blockage of autophagosome-lysosome fusion	Studies in animals	Induced autophagic activity in old animals	Unknown specificity and safety of the target	18
Rapamycin (sirolimus)	mTORC1 inhibition	Animals; also used clinically for immunosuppression	Increased longevity in mice; autophagy-related clearance in models	Dose and time dependency; immunosuppressive and other side effects; unknown effect in humans	19
Enhancing of autophagy/mitophagy	Mitochondria quality regulation through mitophagy	Model organisms; in vitro studies	Reduced accumulation of damaged mitochondria and lower cellular stress	Strength of the evidence differs between different systems; similar to other stress response pathways	34
Telomerase gene therapy/reconstitution	Telomeres' maintenance by TERT	Mouse models	Rescue of telomere shortening and better tissue outcomes in cited mouse models	Cancer risk trade-offs; tissue specificity; translatability to humans is unknown	15
CRISPR-based gene editing (including CRISPRa)	Target-specific gene editing/modulation (for example, TERT up-regulation)	Cellular models; preliminary pre-clinical research	Longer replicative cellular lifespan in the cellular models due to TERT upregulation	Delivery, off-targeting effects, immune response, and safety issues	16

ing/biofabrication to examine the effects of long-term inhibition of the mTOR pathway by rapamycin in terms of cellular stress, autophagy, and telomere maintenance[37].

There is still much work to do with CRISPR technology before beginning human experiments for anti-aging interventions[30]. Despite the fact that CRISPR-Cas9 systems allow precise genome editing and control of gene expression, the development of aging therapies needs to be supplemented with the development of effective delivery, careful evaluation of off-target effects, and screeners for possible negative consequences (immune reactions, cell reprogramming)[31,32].

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