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REVIEW ARTICLE

Telomere and its role in the aging pathways: telomere shortening, cell senescence and mitochondria dysfunction

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Abstract Aging is a biological process characterized by a progressive functional decline in tissues and organs, which eventually leads to mortality. Telomeres, the repetitive DNA repeat sequences at the end of linear eukaryotic chromosomes protecting chromosome ends from degradation and illegitimate recombination, play a crucial role in cell fate and aging. Due to the mechanism of replication, telomeres shorten as cells proliferate, which consequently contributes to cellular senescence and mitochondrial dysfunction. Cells are the basic unit of organismal structure and function, and mitochondria are the powerhouse and metabolic center of cells. Therefore, cellular senescence and mitochondrial dysfunction would result in tissue or organ degeneration and dysfunction followed by somatic aging through multiple pathways. In this review, we summarized the main mechanisms of cellular senescence, mitochondrial malfunction and aging triggered by telomere attrition. Understanding the molecular mechanisms involved in the aging process may elicit new strategies for improving health and extending lifespan.

Keywords Telomere · Telomere shortening · Cellular senescence · Mitochondrial dysfunction · Aging

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Introduction

Mammalian telomeres consist of long tracts of TTAGGG repeats that range from 5 kb in human cells to 100 kb in mice and associated protein complex termed shelterin (de Lange 2005a; McElligott and Wellinger 1997). The main function of telomeres is to protect chromosome ends from being recognized as double-strand DNA damage through recruitment of shelterin, alteration of their structure and compaction of telomere chromatin. These protection mechanisms are based on the maintenance of telomere length. However, telomeres progressively shorten with cell division due to the "end-replication problem" and telomere end processing (Olovnikov 1973; Watson 1972; Wu et al. 2012). When a critical telomere length is reached, shelterin will lose its binding site and telomeric DNA cannot form a protective secondary structure. Aging is characterized by a progressive time-dependent functional decline. Although its

biological causes remain largely unknown, recent studies have identified several hallmarks of aging, which have been divided into three categories including primary causes of aging-associated damage, antagonistic responses to the damage and the integrative hallmarks that are the consequences of the response. Although cellular senescence and mitochondrial malfunction are also hallmarks of aging, telomere attrition has been considered as the primary hallmark (Lopez-Otin et al. 2013; McHugh and Gil 2018). Cellular senescence has been defined as proliferative arrest which decreases the number of cells on the basis of the organism. Furthermore, when senescence occurs in the stem cells, the potential of tissue regeneration will decrease, which contributes to aging. Cellular senescence is initiated by different stimuli, such as telomere dysfunction, oxidative, and oncogenic stress. Distinct triggers induce different modes of cell senescence, mainly including replicative senescence and stress-induced premature senescence (SIPS) (Hernandez-Segura et al. 2018). In this article, we primarily center on cell senescence activated by telomere shortening, known as replicative senescence. Mitochondrial dysfunction can influence the metabolism and activity of cells due to the inefficiency of the respiratory chain. Both of two aging hallmarks, cellular senescence and mitochondrial dysfunction, can be mediated by telomeres shortening (Sahin et al. 2011). Telomere shortening has been connected with aging for many decades, but the molecular mechanism is not particularly clear. In this review, we begin by describing the important role of telomeres in chromosome end protection. Then, we focus on the pathways by which telomeres attrition contributes to aging. Although there are several new articles similar to the topic of this review, our article focuses more on the aging pathways initiated by telomere shortening (Birch et al. 2018; de Magalhaes and Passos 2018; Zole and Ranka 2018). In this article, we summarized two main molecular mechanistic pathways, the telomere-cellular senescence-aging axis and telomere-mitochondria dysfunction-aging axis. Finally, we provide possible anti-aging approaches based on the mechanisms by which telomere attrition promotes aging.

Structure and function of telomere

The natural ends of linear chromosomes are toxic to mammalian cells in that they can be recognized as DNA double-strand breaks, resulting in deleterious chromosomal rearrangement and genomic instability (Lazzerini-Denchi and Sfeir 2016; Xu et al. 2013). This problem was first proposed by Barbara McClintock and Herman Muller, who speculated that specialized structures named telomeres may protect chromosome ends from aberrant DNA repair (McClintock 1941). Telomeres are dynamic chromosome-end complexes, composed of tandem repetitive DNA sequences and associated protective proteins (Blackburn et al. 2015; Muller 1938). Interactions between telomeric DNA and shelterin complexes safeguard chromosome ends from the DNA damage response (DDR) and maintain genome stability (de Lange 2005b).

Telomere DNA

In mammals, telomeric DNA is composed of tandem TTAGGG repeats, which end in single-stranded G-rich 3′ overhangs, known as G-overhangs (Makarov et al. 1997; Moyzis et al. 1988). The G-overhang can invade the double-stranded telomeric DNA forming a lariat-like structure called the t-loop, which has been observed in functional telomeres by electron microscopy and stochastic optical reconstruction microscopy (Doksani et al. 2013; Griffith et al. 1999). By generating t-loops, telomeres can fold into a closed configuration that protects the chromosome ends from being identified as DNA double-strand breaks by the DNA damage repair machinery (de Lange 2009; Morgan et al. 2018).

Telomeric DNA also has a propensity to fold into nocanonical secondary structures, called G-quadruplexes (G4) (Schaffitzel et al. 2001). Studies have reported that G4 structures at the telomeric overhang play an important role in capping telomeres to preserve chromosomal integrity and suppressing the DNA damage signals in telomeres (Ray et al. 2014; Smith et al. 2011). Furthermore, the telomeric G4 structure has been shown to restrain telomere extension by influencing telomerase activity (Oganesian et al. 2006; Zahler et al. 1991). Telomerase is a ribonucleoprotein (RNP) complex, the catalytic core of which comprises telomerase reverse transcriptase

(TERT) and a telomerase RNA (TR). To extend telomeres, telomerase binds to the 3′ end of the DNA and uses its internal RNA as a template for a TERT-catalyzed reverse transcription reaction (Greider and Blackburn 1989; Jiang et al. 2018; Wu et al. 2017). Computational analysis has revealed that the G4 structures are highly distributed in key regulatory regions of the human genome, such as promoters, transcription start sites and telomeres (Bedrat et al. 2016; Chambers et al. 2015; Huppert and Balasubramanian 2005). G4 has been proposed to have regulatory roles in DNA replication, transcription and translation (Hansel-Hertsch et al. 2017; Rhodes and Lipps 2015).

Recent studies have revealed that telomeric DNA is transcribed by RNA polymerase II into long noncoding telomeric repeat-containing RNA (TERRA) from subtelomeric regions to the telomeric repeat sequences (Azzalin et al. 2007; Schoeftner and Blasco 2008). TERRA has been identified as an integral component of telomeric heterochromatin, which is considered a molecular scaffold for various protein enzymes supporting several important functions at chromosome ends (Azzalin and Lingner 2015). In previous studies, decreasing TERRA by different means results in a dramatic loss of telomere sequences and DDR, indicating that TERRA plays an essential role in maintaining telomeric integrity (Chu et al. 2017; Montero et al. 2016). Research has shown that TERRA can bind TERT and base pairs with telomerase RNA template, inhibiting telomerase activity (Redon et al. 2010). Furthermore, whether TERRA increases or decreases, telomerase shows the opposite relationship in studies (Chu et al. 2017; Law et al. 2010; Webb and Zakian 2016). However, recent evidence has suggested that TERRA is involved in telomerase recruitment to telomeres promoting telomerase-mediated telomere elongation, which is contradictory to the conclusions other studies have made (Moravec et al. 2016). Thus, further studies should be conducted to explore the correlation between TERRA and telomerase. It is well known that in telomerase-negative cells, critically short telomeres can be repaired by homology-directed repair (HDR) to prevent early onset senescence (Abdallah et al. 2009; Fallet et al. 2014). Recent studies have proposed that TERRA can form R loops, and the elevated R-loops were correlated with an increase in telomere recombination events (Kar et al. 2016; Rippe and Luke 2015; Sagie et al. 2017). Therefore, it is speculated that TERRA R-loops at critically short telomeres can activate the DDR to promote HDR to prevent senescence (Graf et al. 2017; Yu et al. 2014). Finally, serving as a scaffold, TERRA interacts with telomere repeat factors and heterochromatin protein playing an important role in telomere structural maintenance and heterochromatin formation (Deng et al. 2009).

Shelterin

Telomeric DNA can also recruit shelterin to protect chromosome ends. Shelterin binds specifically to telomeric DNA, which is composed of six proteins: telomeric repeat binding factor 1 (TRF1), TRF2, repressor/activator protein (RAP1), protection of telomeres protein (POT1), TRF1-interacting nuclear protein 2 (TIN2) and TIN2- and POT1-interacting protein (TPP1) (de Lange 2005a; Lazzerini-Denchi and Sfeir 2016). In this review, we divide the function of shelterin into three categories. First, shelterin is thought to protect telomeres via affecting the structure of telomeric DNA. It is proposed that TRF2 represses the ataxia telangiectasia-mutated (ATM)-dependent DNA damage signaling pathway and classical nonhomologous end joining (NHEJ) by folding telomeric DNA into a t-loop (Benarroch-Popivker et al. 2016; Doksani et al. 2013). In addition, recent evidence has revealed that TRF2 and RAP1 are required to repress t-loop cleavage through preventing the activation of poly(ADP-ribose) polymerase 1 (PARP1, one of the DDR factors) to protect telomeres from homologous recombination-mediated repair in mammals (Rai et al. 2016). TRF2 also mediates t-loop unwinding to allow telomerase access to the chromosome end and avoid replication fork collisions in S-phase (Sarek et al. 2016). However, uncontrolled TRF2 stimulates the invasion of TERRA into telomeric double-strand DNA, resulting in the formation of telomeric RNA–DNA hybrids (telR loops), and TRF1 can directly support end protection by restraining telR loops (Lee et al. 2018). G4 structures are considered telomeric replication barriers, and TRF1 may remove these barriers by recruiting helicases, facilitating telomeric replication (Sfeir et al. 2009). Second, shelterin complexes can directly prevent telomeres from DDR. Studies have found that telomeres are likely threatened by the ataxia-telangiectasia mutated and Rad3-related protein (ATR)-dependent DDR, even

they are in the t-loop configuration, and POT1–TPP1 is required to block the activation of the ATR kinase (Kibe et al. 2016). POT1 also contributes to telomere protection by preventing replication protein A (RPA), which is a crucial factor for the activation of ATR binding at telomeres (Zou and Elledge 2003). As the central hub of the shelterin complex, TIN2 plays an important role in repressing ATR and ATM signaling by linking the POT1–TPP1 heterodimer and stabilizing TRF2 at the telomeres (Frescas and de Lange 2014; Hu et al. 2017; Takai et al. 2011). Finally, shelterin is also crucial for the maintenance of telomeric DNA through modulating telomerase activity. Binding tightly to 3′ overhangs, POT1 serves as a negative regulator of telomerase, and a current model proposed that POT1 and TPP1 compete with telomerase for access to the 3′ telomere terminus (Kelleher et al. 2005; Lei et al. 2005; Loayza 2003). TIN-tethered TPP1 recruits both POT1 and telomerase to telomeres (Abreu et al. 2010; Nandakumar et al. 2012; Xin 2007). TIN2 is required for the recruitment of TPP1/POT1, and telomerase decreases with knockdown of TIN2. Recent studies have suggested that TIN2 mutation decreases the frequency of telomere extension by telomerase, suggestive of a TPP1-independent role of TIN2 in telomere regulation (Frank et al. 2015; Nandakumar et al. 2012; Takai et al. 2017). Studies have suggested that POT1–TPP1 enhances telomerase processivity. The questions remain how POT1, a negative regulator of telomerase, interacts with TPP1 to promote telomerase processivity (Latrick and Cech 2010; Wang et al. 2007) (Fig. 1).

Telomere chromatin compaction

In the above description, we summarized how telomere components: shelterin subunits and telomeric DNA protect telomere and maintain its integrity. Several observations have shown that robust protection mechanisms must exist at chromosome ends. A recent study indicates that telomeres are condensed into tight globular structures in vivo between shelterin subunits and telomeric DNA, and the compaction of telomeric chromatin plays a major role in protecting telomeres against DDR signaling through inhibiting the DDR signal at telomeric sites (Bandaria et al. 2016). In summary, the most important function of telomere is to ensure chromosome stability. The realization of this function depends on not only telomere-associated proteins, but also the secondary protective structures of telomere DNA formation and the compaction of telomeric chromatin. Only when all parts function properly, can telomeres maintain their integrity.

Telomere-cellular senescence-aging axis

Telomere attrition

DNA is duplicated through semiconservative replication in that each strand of the original parental doubled-stranded DNA serves as a template for the reproduction of the complementary strand, and DNA replication can proceed in only one direction, from the 5′ end to 3′ end. For the leading strand, DNA is copied continuously in the direction of the advancing replication fork. For the lagging strand, which is assembled via the joining of Okazaki fragments, DNA replication proceeds discontinuously. Okazaki fragment synthesis requires an RNA primer, which is synthesized by RNA polymerase, because DNA polymerase can only continue (but not begin) a strand. After Okazaki fragments are synthesized, DNA polymerase I removes the RNA primers and then fills in the internal gaps with DNA. Okazaki fragments are subsequently connected by ligase. However, without primer, a short gap will be left on the lagging strand at the end of chromosome after removal of the RNA primer. Thus, the telomere gets shorter after multiple rounds of DNA replication. This is the "end-replication problem" proposed by Watson in 1972 (Olovnikov 1973; Sugino et al. 1972; Watson 1972). However, this incomplete replication is not the only reason why telomeres shorten. After replication, the formation of the G overhang occurs at leading-end telomeres through 5′ end resection, which could make a significant contribution to telomere attrition (Wu et al. 2012). Except the end replication problem and telomere 5′ end resection, telomere attrition rates are correlated with many other factors, such as reactive oxygen species (ROS), which could accelerate telomere shortening (Herbert et al. 2008). Although telomeres protect mammalian chromosome ends from being recognized as broken ends through altered structure and shelterin complexes, this framework cannot be maintained as telomeres shorten. As telomeres shorten, they gradually lose the ability to recruit sufficient shelterin

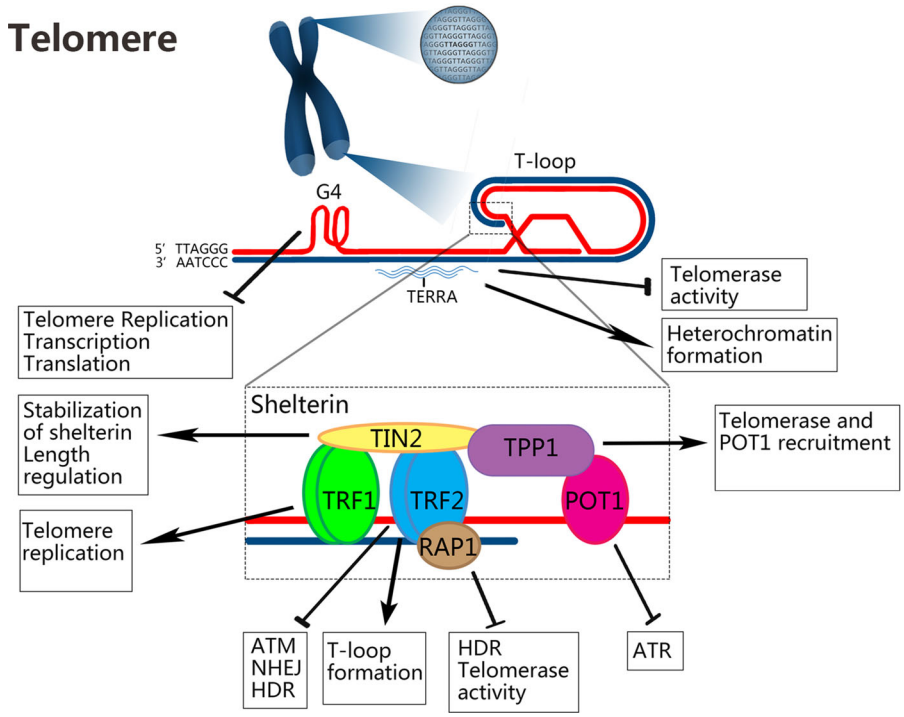

Fig. 1 Telomere structure and function. Telomeres are composed of repetitive sequence TTAGGG and associated protective proteins, shelterin. Telomeric DNA ends in a single-stranded overhangs, which invade the double-stranded region of telomeres to form a lariat-like protective, T-loop. Telomeric DNA repetitive sequences also can fold into non-canonial secondary structures, G-quadruplexes and can be transcribed into TERRA. Telomeric DNA is bound by telomere-specific proteins, shelterin, which consist of TRF1, TRF2, RAP1, TIN2, TPP1 and POT1. The altered telomeres structure and shelterin complex are essential for the maintenance and integrity of chromosome ends

components that facilitate the formation of protective telomere secondary structures such as t-loops which repress the ATM and ATR pathways (Erdel et al. 2017; Gaullier et al. 2016; Smogorzewska et al. 2000).

Telomere attrition and cellular senescence

The first scientist to connect the Hayflick limit with telomere replication was Olovnikov. He proposed that telomere length could determine the possible number of cell division rounds (Olovnikov 1973). In 1986, telomeres were directly linked to cell aging by Cooke and Smith when they compared telomere length in different tissues (Cooke and Smith 1986). Over the next few years, researchers found that the replicative capacity of human cells increases because telomerase extends the telomeres. These experiments confirmed that progressive telomeres shortening is indeed the main factor resulting in senescence (Allsopp et al. 1992; Harley et al. 1992). Thus, telomeres are regarded as the "molecular clock" of cells (Muezzinler et al. 2013). Telomeres lose their protective structure and proteins as they gradually shorten and then trigger replicative senescence through DDR pathways (Morgan et al. 2018).

Cellular senescence is defined as a stable cell cycle arrest, which is established and maintained by at least two major pathways: the p53-p21 and p16-Rb pathways (Childs et al. 2015; He and Sharpless 2017; Munoz-Espin and Serrano 2014). Here, we focus on the replicative senescence caused by telomere shrinking. Without expression of telomerase in somatic cells, telomeres shorten with every round of replication, and short telomeres will be detected as double-strand DNA breaks when critical telomere shortening is reached (Arnoult and Karlseder 2015; d'Adda di Fagagna 2008). DNA double-strand breaks induce DDR, a signaling cascade converging on the ATM kinase that activates p53 (Lossaint et al. 2011; Roake and Artandi 2017; Wang et al. 2011). P53 is a canonical tumor

suppressor that is heavily regulated by posttranscriptional modification, and it is inactive in most tumors and upregulated in senescent cells (Itahana et al. 2001). P21 is the first identified downstream target of p53, and it can inhibit Cdk2 to block pRb phosphorylation. Hypophosphorylated Rb can bind to E2Fs transcription factors, thus preventing them from activating transcription genes associated with cell proliferation to result in cell cycle arrest in the G1 phase (Beausejour et al. 2003; Harper et al. 1993; Shay et al. 1991; Xiong et al. 1993).

With each round of cell division, telomeres continuously shrink to a critical length, and cells enter replicative senescence. However, there are some kinds of cells such as germline cells, stem cells and cancer cells that divide continuously without limit. This fact was the opposite of what had been predicted. In fact, the key to maintaining telomere length in these cells is telomerase, which provides a solution to the end-replication problem (Borah et al. 2015; Kim et al. 1994; Morin 1989). As was described previously, shelterin complex recruits telomerase to the telomeres and promotes processive telomere elongation. Therefore, the majority of human cancer cells expressing telomerase can bypass the Hayflick limit to become immortal. Although telomerase is also expressed in many human cells such as embryonic (ES) cells and most adult stem cells, it is not sufficient to compensate for telomere attrition as cells grow, and thus, telomere shrinking compromises cells proliferating with age in most tissues (Alder et al. 2015; Harley et al. 1990; Wang et al. 2016).

Senescence-associated aging

Many studies have shown a strong correlation between telomere length and aging. For example, reversing the function or length of telomeres in mice would improve mouse life span, and telomerase gene therapy can reverse premature aging and delay physical aging in mice (Armanios et al. 2009; Bernardes de Jesus et al. 2012; Derevyanko et al. 2017; Steenstrup et al. 2017). Telomere theory proposes that telomere shortening is the trigger for aging. However, it remains uncertain how telomeres lead to aging in organisms. Telomere attrition is regarded as the primary hallmark of aging or the cause of age-associated damage resulting in cellular senescence (Lopez-Otin et al. 2013). Cellular senescence, a hallmark of aging, can in turn induce consequential aging (McHugh and Gil 2017). Therefore, telomere shortening can drive aging through cellular senescence.

Although there is not insufficient evidence showing a causal association between cellular senescence and aging, emerging evidence has shown that cellular senescence leads to age-related tissue dysfunction through two key mechanisms, namely, stem cell exhaustion and senescence-associated secretory phenotype (SASP). Stem cells can maintain tissue homeostasis through renewing the impaired cells, whose function can be affected in both cell-autonomous and cell-nonautonomous manner. The overall decrease in the regenerative ability of tissues is one of the most common characteristics of aging. The prominent manner promoting the decline in tissue regenerative potential is persistent cell-autonomous growth arrest in stem cells (Flores et al. 2005; Sharpless and Depinho 2007). The induction of senescence in stem cells leads to its exhaustion and decline in function, which in turn compromises tissue deterioration. For instance, a cell-autonomous loss of stem cell self-renewal in skeletal muscle results in a great decline in skeletal muscle function and regenerative capacity (Bernet et al. 2014). Research has revealed that muscle and fat progenitor cells in BubR1 progeroid mice are highly prone to cellular senescence (Baker et al. 2013). Despite the fact that sufficient proliferation of stem or progenitor cells plays a vital role in the maintenance of the organism, most stem or progenitor cells are retained in a quiescent state, in which cells are non-dividing but remain capable of proliferation in response to extrinsic factors. The quiescence is important for stem cells to maintain their long-term repair function for tissues. However, senescent cells can drive stem cells re-enter the cell cycle through SASP, which accelerates the exhaustion of stem cell (Cosgrove et al. 2014; Rera et al. 2011; Sousa-Victor et al. 2014).

In addition to affecting stem cells by establishing a persistent growth arrest, senescence could also perturb the specialized microenvironment, or niche, on which the optimal function of stem cells depends nonautonomously through the SASP (Brack et al. 2007; Jang et al. 2011; Pricola et al. 2009). Senescent cells secrete hundreds of factors manifesting dramatic alterations in their secretome termed the "SASP", which is enriched in proinflammatory cytokines, chemokine growth factors and proteases (Coppe et al. 2010; Kuilman

and Peeper 2009). Emerging studies utilizing genetic systems or drugs deleting senescent cells show that the clearance of senescent cells attenuates inflammation and creates a proregenerative environment (Jeon et al. 2017). Moreover, many studies have discovered that the regenerative potential of old stem cells was markedly improved by exposure to a young systemic environment (Brack et al. 2007; Conboy et al. 2005). It is proposed that senescent cells also affect neighboring cells in a paracrine manner, in which senescent cells secrete IL-1β, TGFβ and certain chemokine ligands spreading the senescence phenotype to surrounding cells to reinforce age-related tissue deterioration (Acosta et al. 2013; Nelson et al. 2012). Recent reviews proposed a tissue remodeling model in which the SASP can recruit immune cells to clear the senescent cells and inflammatory factors and then progenitor cells repopulate and regenerate the damaged tissue. However, this function of clearance and regeneration declines with age, which leads to aberrant tissue architecture due to the accumulation of senescent cells and inflammatory factors in the tissue (Munoz-Espin and Serrano 2014). Specific components of SASP, IL-6 and IL-8, may also stimulate epithelial tissue fibrosis by inducing epithelial-mesenchymal transition (Laberge et al. 2012; Parrinello et al. 2005). In addition, proteases secreted by senescent cells may induce tissue structural changes via cleaving extracellular matrix proteins, signaling ligands or other components in the tissue microenvironment (Parrinello et al. 2005; Zhang et al. 2007). Studies have shown that the clearance of senescent cells reduces levels of the chronic inflammatory markers, IL-6 and IL-1β, in aged kidney, heart, liver, spleen, lung and osteoarthritic knee, which suggests that the SASP is partially lei behind chronic inflammation, also termed as inflammaging (Baker et al. 2016; Jeon et al. 2017). The intimate correlation between chronic inflammation and aging phenotypes such as frailty and age-related diseases has been supported by many studies (Balestro et al. 2016; Franceschi and Campisi 2014; Soysal et al. 2016). Although the SASP can recruit immune cells to eliminate senescent cells, the adaptive immune system shows a decline with aging, which is termed immunosenescence (Nikolich-Zugich 2018). The decline in the function of the immune system may result from hematopoietic stem cell dysfunction (Sahin et al. 2011). Senescent cells secreting inflammatory factors to promote senescence in an autocrine or a paracrine manner as well as a decrease in their clearance may be the reason for the accumulation of senescent cells during aging (He and Sharpless 2017). It is believed that the accumulative senescent cells can promote chronic inflammation through the secretion of proinflammatory growth factors, cytokines and chemokines and occupy key cellular niches, eventually impairing tissue homeostasis and contributing to aging (He and Sharpless 2017; Lawless et al. 2010; van Deursen 2014) (Fig. 2).

Therefore, cellular senescence exerts a profound influence on the aging process via various mechanisms. Here, we reviewed two main factors. On one hand, cellular senescence leads to stem cell exhaustion, which then reduces the regeneration capacity of

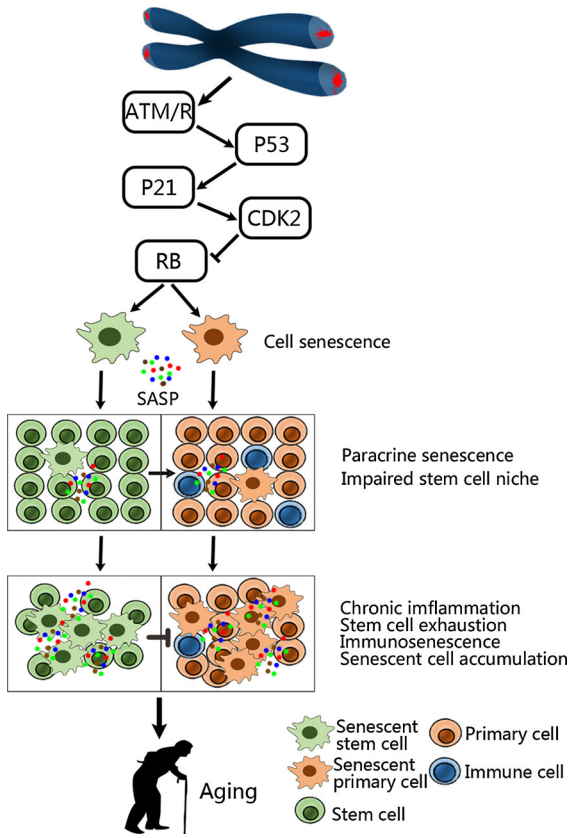

Fig. 2 Mechanisms of senescence-associated aging induced by telomere dysfunction. Telomere shortens with cell proliferation and the critically short telomeres could be recognized as double-strand DNA damage which activates p53 then resulting in cellular senescence through the repression of RB. Cellular senescence leads to exhaustion and function decline of stem cell and chronic inflammation in tissue which ultimately drive aging

tissues. On the other hand, senescent cells secrete a series of factors including proinflammatory cytokines, chemokines, growth factors, and proteases which could exacerbate potentially deleterious inflammatory responses and destroy the environment in which stem cells function.

Telomere-mitochondria-aging axis

Telomere shortening and mitochondrial dysfunction

Telomere shortening and mitochondrial dysfunction have long been considered to be a prime initiation factor of natural aging. Although there are many theories that explain how they affect the aging process, these theories do not take into consideration the relationship between them. However, emerging evidence indicates the existence of a strong linkage between telomere attrition and metabolic compromise. In the previous section, we discussed how telomere shortening promotes the aging process through cellular aging. Recent studies have shown that telomere shortening can also affect mitochondria activity via multiple ways to initiate the aging process. In this section, our attention was focused on mitochondria dysfunction and dysregulated metabolic processes induced by telomere attrition. The signaling from the nucleus to mitochondria through the peroxisome proliferator-activated receptor gamma co-activator 1α/β (PGC-1α/β, the master regulators of mitochondrial biogenesis and function) establishes the connection between telomere shortening and mitochondria malfunction (Fang et al. 2016). When DNA damage occurs due to telomere dysfunction, p53 and DDR pathways are activated, which in turn suppress PGC-1α and PGC-1β, consequently leading to mitochondrial dysfunction (Dabrowska et al. 2015; Sahin et al. 2011). Moreover, research has found that overexpression of PGC-1α can reverse aging muscle to younger muscle at the molecular level and plays a significant role in longevity (Garcia et al. 2018). Another prominent pathway linking telomere attrition to mitochondria dysfunction is the NAD^+-SIRT1-PGC-1α axis. In this axis, short telomeres are sensed as doubled-strand breaks by nicotinamide adenine dinucleotide ($NAD^{+)}$-dependent PARP1, which can initiate DNA repair signaling, a process that requires consumption of NAD^+. PARP1 hyperactivation results in NAD^+ consumption, hence limiting the NAD^+-dependent deacetyase sirtuin 1 (SIRT1) activity (Fang 2014; Gibson and Kraus 2012). SIRT1 has been found to increase mitochondrial function and biogenesis through transcription factor PGC-1α and thereby loss of SIRT1 activity could contribute to mitochondria dysfunction, particularly in muscle (Fang 2014; Rodgers et al. 2005). In addition to the NAD^+-SIRT1-PGC-1α axis, SIRT1 also has been proposed to inhibit mitochondrial transcription factor A (TFAM) via the SIRT1-HIF-1α-Myc-TFAM pathway, independently of PGC-1α, increasing mitochondrial compromise (Gomes et al. 2013). Heap of evidence suggests that the role of telomere attrition in ageing has been linked to the decreased mitochondrial biogenesis and function. However, the emerging study indicates that telomere shortening may also have an impact on the aging process via increasing mitochondria biogenesis. In this study, researchers proposed that the activation of ATM due to DNA damage activates AKT and mechanistic target of rapamycin complex 1 (mTORC1), resulting in PGC-1β-dependent mitochondrial biogenesis and ROS generation (Correia-Melo et al. 2016). Therefore, whether the mitochondrial synthesis is too much or too little will lead to the dysfunction of mitochondria. Only when the mitochondria biogenesis maintains homeostasis, can the mitochondria perform its optimal function (Fig. 3).

Mitochondrial dysfunction-related aging

In the previous section, we summarized telomere shortening leads to mitochondrial dysfunction through multiple pathways. Mitochondria are crucial for energy generation, producing adenosine triphosphate (ATP) through oxidative phosphorylation and also play an essential role in cell metabolic homeostasis, signaling, differentiation and senescence (Fang et al. 2016; Kauppila et al. 2017). Thus, the malfunction of mitochondria will bring about decreased ATP production, increased ROS generation, diminished antioxidant defense and metabolic disorders.

Impaired mitochondrial function and alterations of mitochondrial biogenesis have been linked to key aspects of the aging process, including cellular senescence, the decline in stem cell activity and chronic inflammation (Kauppila et al. 2017; Sun et al.

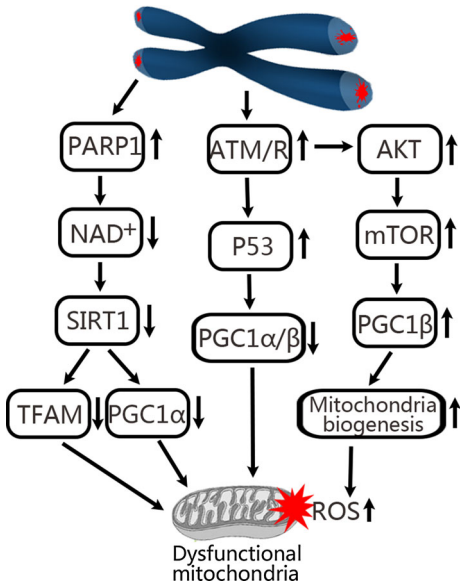

Fig. 3 Telomere dysfunction regulates the biogenesis and function of mitochondria. Telomere attrition modulates mitochondrial biogenesis and function via PARP1-NAD^+-SIRT1, ATM/R-P53-PGC1α/β and ATM-AKT-mTOR-PGC1β pathways. The activation of these three pathways eventually results in mitochondrial dysfunction and the increased ROS

2016). Here, we reviewed how mitochondria dysfunction promotes aging through impacting on these key aspects. Mitochondrial dysfunction has been related to the perturbation of metabolic homeostasis, including gluconeogenesis, fatty acid metabolism and β-oxidation which are the basis of cell survival. Decline in cell function is believed to be a result from dysregulated metabolism which could promote cellular senescence through multiple pathways (Sui et al. 2016; Wiley and Campisi 2016). Many studies have suggested that mitochondrial dysfunction induces cellular senescence through different pathways. It is well known that excessive ROS, which is generated by mitochondria, plays a critical role in cellular senescence (Colavitti and Finkel 2005; Frankel et al. 2013). In addition to driving senescence, evidence has also shown that the excessive production of ROS due to telomere shortening can stabilize the DDR and maintain persistent cellular senescence (Correia-Melo et al. 2016). Decreased ATP production in dysfunctional mitochondria increases the adenosine monophosphate (AMP)-to-ATP ratio that promotes cellular senescence through stimulating AMP-activated protein kinase (AMPK), which is a central mediator of cellular metabolism (Mihaylova and Shaw 2011; Zwerschke et al. 2003). Furthermore, recent studies have proposed a mitochondrial dysfunction-associated senescence (MiDAS) and revealed a mechanism by which mitochondrial malfunction can improve the aging process. This study suggested that compromised mitochondria decreased NAD^+/NADH ratios, resulting in MiDAS via activating AMPK, which induces a p53-dependent senescence, and revealed that mitochondrial dysfunction induces aging phenotypes through distinct SASP components such as IL-10, CCL27, TNFα and HMB1, which affect surrounding cells in a paracrine manner (Davalos et al. 2013; Frankel et al. 2013; Wiley et al. 2016). Due to the opinion that functional decline of stem cells is closely related to aging, there is increasing interest in the relationship between mitochondrial dysfunction and stem cell function (Lopez-Otin et al. 2013). Recent studies have shown that increasing ROS can trigger hematopoietic stem cell and progenitor entry into the cell cycle and ultimately stem cell exhaustion due to the decreased capacity for self-renewal (Maryanovich et al. 2015). As the center of metabolism, emerging evidence indicated that mitochondrial metabolism also plays a critical role in the self-renewal and differentiation of stem cells (Chandel et al. 2016; Ito and Suda 2014). It is known that quiescent stem cells maintain basal metabolic activity through glycolysis and low respiratory activity and metabolic disorder predicatively leads to stem cell dysfunction (Takubo et al. 2013). The mitochondrial respiratory chain is also essential for maintaining fetal Hematopoietic stem cell (HSC) differentiation into progenitor and adult HSC quiescence. Therefore, respiratory impairment induced by mitochondrial dysfunction will cause a defect in HSC differentiation, which then leads to loss of quiescence and entry into the cell cycle giving rise to an exhausted progenitor cell pool and lethality (Anso et al. 2017). A decrease in NAD^+ levels contributing to aging phenotypes has been reported by many studies, and evidence has also been found showing that increased mitochondrial NAD^+ levels delay stem cell senescence and improve life span in mammals (Prolla and Denu 2014; Son et al. 2016; Verdin 2015; Zhang et al. 2016). Mitochondrial malfunction also affects another hallmark of aging, chronic inflammation. One of the most common mechanisms of chronic inflammation is oxidative stress as a consequence of excessive generation of ROS, which can elicit further mitochondrial

dysfunction and ROS generation, forming a vicious circle of oxidative damage. Mechanistically, a recent study has found that telomere attrition caused severe inflammation primarily based on hyperactivation of the NLRP3 inflammasome through mitochondrial oxidative stress (Kang et al. 2018). Taken together, this article indicates that mitochondrial dysfunction induced by telomere attrition contributes to the aging process through cellular senescence, stem cell function decline and chronic inflammation (Fig. 4).

Conclusions and future directions

Increasing evidence has suggested that the loss of telomere repeats in cells contributes to human aging.

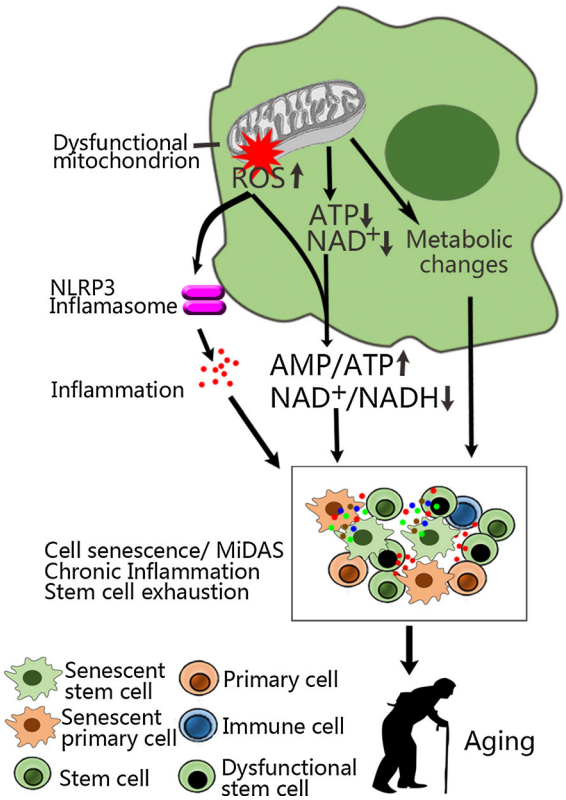

Fig. 4 A model of mitochondrial compromise-related aging elicited by telomere attrition. In this model, telomere attrition-induced mitochondrial dysfunction leads to defective ATP generation, NAD^+ reduction, increased levels of ROS and metabolic changes which regulate multiple pathways in cells. Consequently, the activation of these pathways triggered by mitochondrial dysfunction gives rise to stem cell exhaustion and inflammation in tissue and drive aging

Here, we reviewed the main mechanisms involved in the protection of chromosome ends and the role of telomere shortening in the aging process. We conclude that altered telomere structure, shelterin complexes and compact telomeric chromatin together protect chromosome ends and telomere attrition promotes aging through initiating cellular senescence and mitochondrial malfunction. Although telomere shortening has been considered a primary hallmark of aging, the model of aging in this article cannot explain the aging process exactly because the average telomere length shows great variation between individuals of the same age. Furthermore, it is still a challenge to understand the exact mechanisms by which cellular senescence and mitochondria drive aging directly.

Deciphering the aging model proposed in this article could advance the development of antiaging interventions. In this aging network, telomere shortening is the primary molecular cause of aging, and thus, telomere is an important interventional target for anti-aging. Critically short telomeres owing to telomerase deficiency can be rescued by telomerase activation. In recent years, several telomerase-based antiaging strategies have developed, mainly including chemical telomerase activator, telomerase expression activator and telomerase gene therapy. Contemporary evidence indicates that TA-65, a small molecule activator, can restore telomere length and improve the health span of mice without increasing cancer incidence (Bernardes de Jesus et al. 2011). In addition to activating telomerase directly, studies found that sex hormones, TERT transcription activator, also rescue telomere shortening and extend mice life span (Bar et al. 2015; Calado et al. 2009). More recently, evidence has suggested that the reactivation of telomerase activity by gene therapy is sufficient to extend mouse longevity and delay aging without increasing cancer (Bernardes de Jesus et al. 2012). However, constitutive telomerase expression is a feature of almost all cancer cells. Considering their ability to induce cancer, telomerase-based interventions should be taken with caution (Bar and Blasco 2016). Because increasing senescent cells and inflammation play a prominent role in the aging process, clearing senescent cells and attenuating the SASP have been regarded as important strategies towards anti-aging. There is increasing evidence that the elimination of senescent cells using senolytics, small molecules that specifically ablate senescent cells, augments organ function

and mice lifespan (Baker et al. 2011; Jeon et al. 2017; Zhu et al. 2015). Several effective SASP suppressors such as rapamycin, metformin and sirtuin activator have been shown to alleviate age-related tissue deterioration and extend prolong life-span (Herranz et al. 2015; Hitchings et al. 2015; Laberge et al. 2015; Nakamaru et al. 2009). Mitochondrial compromise plays a crucial role in aging pathway, and thus, rescuing function of mitochondria may be an effective method to combat aging. From the pathways we have summarized, it is feasible to improve mitochondria function via activating SIRT1, which is considered to be a promising target for slowing down aging process (Grabowska et al. 2017). Increasing evidences have proposed that caloric restriction and physical exercise promote mitochondrial biogenesis and function through activation of SIRT1 (Cohen et al. 2004; Rodgers et al. 2005). As a NAD^+-dependent enzyme, SIRT1 activity is also improved by NAD^+ repletion (Zhang et al. 2016). While the increased generation of ROS is the major feature of mitochondrial compromise, the utilization of anti-oxidants, N-acetyl cysteine (NAC), has been demonstrated to ameliorate the adverse effect of ROS. Since mTOR causes the PGC-1β-dependent ROS production, the inhibitor of mTOR such as metformin and rapamycin can also reduce ROS (Barzilai et al. 2016; Laplante and Sabatini 2012). Stem cells are fundamental to the regeneration of tissue and thus the maintenance of stem cells plays an essential role in tissue function. Emerging evidence has suggested that supplementing stem cell through reprogramming technology or stem cell transplantation has resulted in tissue and organ functional rejuvenation (Copelan 2006; Rocheteau et al. 2015; Wahlestedt et al. 2013). Above all, every key point in the aging process is likely to be an effective antiaging target. Therefore, a comprehensive model and a breakthrough at the molecular level of aging are required for the discovery of antiaging interventions. Exploring the aging process at the molecular level is still a challenge, and understanding this will provide a clearer picture for antiaging therapies.

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

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