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Stress and immunosenescence: the role of telomerase

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Abstract

Chronic stress is associated with the accelerated aging of the immune system and represents a potent risk factor for the development and progression of a wide range of physical and mental disorders. The elucidation of molecular pathways and mechanisms underlying the link between stress and cellular aging is an area of considerable interest and investigation. In this context, telomere biology has emerged as a particularly attractive candidate mechanism. Several studies have linked immune cell telomere length with stress-related conditions and states, and also with several physical and mental disorders. Because the cellular reverse transcriptase enzyme *telomerase* is the primary regulator of telomere length (by adding telomeric DNA to telomeres and thereby attenuating telomere shortening), the understanding of its regulation and regulatory functions constitutes a prime target for developing strategies to prevent, attenuate or reverse the

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adverse consequences of immune system aging (immunosenescence). In this review we provide an overview of the mechanistic pathways linking telomerase with stress and cellular aging, with an emphasis on the immune system. We summarize and synthesize the current state of the literature on immune cell telomerase in different stress- and aging-related disease states and provide recommendations for future research directions.

Keywords

Telomerase; Immunosenescence; hTERT; Inflammation; Oxidative stress; Stress hormones

1. Introduction

Chronic stress is a major contributor to the development and progression of a range of physical and mental disorders such as cardiovascular disease, type 2 diabetes, metabolic syndrome, autoimmune disease and depression (Cohen et al., 2007). Several lines of evidence converge to suggest that these pathophysiological effects of stress on health and disease risk are mediated in large part by rate of accelerated aging of the immune system (immunosenescence). This process is characterized by the inability to mount an appropriate and effective immune response to challenge, and it is associated with a low-grade chronic pro-inflammatory state (Fulop et al., 2017). Many of the immunological changes associated with aging resemble those observed following long-term or chronic stress exposure (Bauer, 2005), including “non-resolving” inflammation and elevated oxidative stress (Epel, 2009; Miller et al., 2014).

The telomere biology system plays a fundamental role in maintaining genomic and cellular and integrity. This system comprises two closely interlinked entities 1) telomeres, the tracts of non-coding tandem repeats of simple DNA sequences [5′-$(TTAGGG)_n$-3′] and shelterin proteins that cap the ends of linear chromosomes, and 2) telomerase, the reverse transcriptase enzyme that adds telomeric DNA to telomeres (Blackburn et al., 2015). The loss of the integrity of telomeres affects the replicative capacity of cells and imposes a self-perpetuating pathway of global epigenetic changes that alter overall chromatin and transcriptional properties, ultimately resulting in cellular senescence and aging (Harrington and Pucci, 2018; Karlseder, 2009; O’Sullivan et al., 2010). A substantial and convergent body of evidence has linked shortened telomeres to several age-related risk factors, earlier mortality (Benetos et al., 2001; Cawthon et al., 2003; Kimura et al., 2008; Martin-Ruiz et al., 2006), non-communicable diseases (D’Mello et al., 2015; Georgin-Lavialle et al., 2010; Haycock et al., 2014; Lindqvist et al., 2015; Tamura et al., 2016) and psychological stress conditions (e.g., chronic stress in adults, childhood traumatic experiences and prenatal stress exposure (Coimbra et al., 2017; Entringer et al., 2018; Mathur et al., 2016; Oliveira et al., 2016)). Most of these associations have been documented in peripheral blood mononuclear cells (PBMCs), the leukocytes that are isolated from whole blood by density gradient centrifugation techniques. Because the enzyme telomerase can counteract telomere shortening and is essential for healthy cell and immune functioning and also is responsive to biological stress mediators, it constitutes a prime target for developing novel strategies to prevent, attenuate or even reverse the adverse consequences of imunosenescence.

In order to facilitate a better understanding of the mechanistic pathways linking telomerase, immunosenescence and stress, we first provide an overview of the regulation and regulatory functions of telomerase. Next, we review, summarize and comment on the current state of the literature concerning PBMC telomerase in different stress- and aging-related states and pathologies (the role of telomerase in the initiation and progression of cancer is beyond the scope of this review and has been extensively discussed elsewhere (Jafri et al., 2016)). We then describe intervention studies related to lifestyle changes that target telomerase, and discuss methodological issues related to the measurement of telomerase expression and activity (e.g., assessment of telomerase from non-stimulated vs. *in vitro* mitogen- stimulated immune cells) that might explain and reconcile some of the inconsistencies in the literature. Finally, we provide some recommendations for future research regarding immune cell telomerase in humans in the context of health and disease risk.

2. The role of telomerase in cell function

Telomeres are the DNA-protein complexes located at both ends of linear chromosomes (Blackburn et al., 2015). In humans, telomeres consist of double-stranded repeats of guanine-rich tandem DNA sequences [5'-(TTACGG)n-3'] that end in a single-stranded 3'-overhang and an attached shelterin protein complex that protects the single-stranded 3'-overhang by providing a secondary structure that facilitates the formation of a nucleotide loop (also referred to as the T-loop). Because conventional DNA polymerase machinery is unable to fully replicate the 3'-ends of the lagging strand, a phenomenon that is referred to as the "end-replication problem", telomeres shorten between approximately 30 to 150 base pairs with each cell replication. After successive mitoses, telomeres reach a critically short length, which makes it more difficult to recruit shelterin proteins. This then results in chromosomal fusions, activation of DNA damage checkpoint responses and genomic instability, and thereby induces cellular apoptosis or activates senescence (Blackburn et al., 2015). Telomerase is a reverse transcriptase enzyme that consists of a RNA component (TR or TERC) and a catalytic protein domain (TERT). Both hTERT and hTERC are essential for the *in vitro* reverse transcriptase activity of the human telomerase enzyme. However, under *in vivo* conditions telomerase consists of additional subunits, including dyskerin, NHP2, NOP10, GAR1 and the ATPases reptin and pontin, all promoting the stability and assembly of a functional telomerase holoenzyme (Jafri et al., 2016; Ozturk et al., 2017). Telomerase is essential for the elongation and maintenance of telomeres, and it does so by adding telomeric repeat sequences to the chromosomal DNA ends and thereby compensating for losses that occur with each round of DNA replication (Artandi and DePinho, 2010; Blackburn, 2005). Telomerase expression varies during development and across cell types. In most somatic cells telomerase activity is almost completely inhibited, whereas in germ cells, stem cells of proliferating tissues and activated immune cells telomerase activity levels are maintained (Forsyth et al., 2002). Telomerase not only maintains and elongates telomere length but also preserves healthy cell function. Through its modulation of intracellular signaling pathways and its interaction with several transcription factors, telomerase promotes the proliferation of resting stem cells, modulates signaling pathways during embryogenesis and normal adult tissue genesis, and protects cellular proliferation capacity and survival under cellular stress conditions and after immune activation (Ale-Agha et al.,

2014; Ozturk et al., 2017). The following section describes how telomerase is regulated and provides an overview of effects of telomerase on cellular and immune function that extend beyond those of telomere lengthening.

2.1. Regulation of telomerase activity

Telomerase is highly regulated by epigenetic, translational and posttranslational mechanisms. In humans, the expression and the activity of the telomerase holoenzyme are regulated through multiple pathways, including transcription, alternative splicing, phosphorylation, protein degradation and cellular localization. Several transcription factors directly influence the promoter region of the hTERT gene. For example, activation of the p53 tumor suppressor protein transcriptionally inhibits telomerase expression. p53 can be activated in response to DNA damage and telomere dysfunction, resulting in growth arrest, DNA repair, senescence or apoptosis (Sahin et al., 2011). Other transcription factors such as E2F-1 and Wilms' tumor 1 tumor suppressor also inhibit hTERT expression (Crowe et al., 2001; Oh et al., 1999), whereas c-Myc, hypoxy-inducible factor-1 (HIF-1), nuclear factor-KB (NF-KB), β-catenin, signal transducer and activator of transcription(STAT)3 and STAT5 up-regulate hTERT expression (Anderson et al., 2006; Hoffmeyer et al., 2012; Sundin and Hentosh, 2012; Wu et al., 1999b; Yin et al., 2000; Zuo et al., 2011). For a complete overview of factors involved in the transcriptional regulation of hTERT we refer to the review by Ramlee et al. 2016 (Ramlee et al., 2016).

The hTERT protein can be phosphorylated at different sites by several kinases. Reversible phosphorylation of hTERT determines its cellular localization and activity level. In lymphocytes hTERT is transported into the nucleus, paralleled by increased nuclear telomerase activity upon activation by antigens (Liu et al., 2001). However, only the phosphorylated form of hTERT can be imported into the nucleus (Akiyama et al., 2004), where it can bind to the other components of the telomerase holoenzyme. Akt, an important kinase in the phosphoinositide 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) signal transduction pathway, phosphorylates hTERT and up-regulates its activity. Heat shock protein 90 (Hsp90), a protein known to form a complex with hTERT, Akt and mTOR, is important in the regulation of telomerase activity and is necessary for its stability and activity (Haendeler et al., 2003; Kawauchi et al., 2005). The PI3K-Akt-mTOR signaling pathway is essential for immune cell proliferation and eliciting normal immune responses (Bu et al., 2007; Kawauchi et al., 2005; Sundin and Hentosh, 2012; Zhao et al., 2008; Zhou et al., 2003). This pathway is regulated by environmental cues in the form of nutrients, growth factors, cytokines and stress. Upon activation, it stimulates protein synthesis, cell growth and proliferation, regulates glucose and fat metabolism, and represses autophagy. Moreover, mTOR is considered an important regulator of immune function because of its role in sensing and integrating cues from the immune microenvironment and its involvement in the proliferation, activation and differentiation of immune cells, mainly by reprogramming metabolic pathways (Powell et al., 2012).

2.2. Telomerase function in mitochondria

Mitochondria are cellular organelles that convert oxygen and nutrients in adenosine triphosphate (ATP), the main source of cellular energy. Mitochondria are a major site for the

generation of reactive oxygen species (ROS) and also the cell organelles most susceptible to ROS-induced damage. Cellular aging is characterized by a decline in mitochondrial respiratory function and ATP production and an increase in ROS-induced mitochondrial DNA mutations, thereby making mitochondrial DNA damage a good indicator of intracellular oxidative stress (Saretzki, 2009). Prolonged exposure to high(er) levels of oxidative stress is associated with shorter telomere length and reduced telomerase activity. Due to the high content of guanine residues, telomeres are highly sensitive to oxidative damage. Oxidative stress accelerates telomere shortening and induces senescence (or apoptosis) via DNA damage-induced activation of the p53 pathway, generating mitochondrial dysfunction, increased ROS concentrations, and consequently further DNA damage (Haendeler et al., 2004; Saretzki, 2009; von Zglinicki, 2002).

Telomerase is essential for normal mitochondrial production and function (Sahin et al., 2011). Several recent reports have examined the transport of hTERT into mitochondria, which appears to be mediated by a mitochondrial import sequence at the N-terminal of hTERT. Accumulating endogenous oxidative stress induces the nuclear export of hTERT to the cytosol and decreases nuclear and total telomerase activity, whereas cytosolic hTERT protein increases in cytosolic fractions. The addition of antioxidants decelerated this process (Haendeler et al., 2004). Mitochondrial hTERT has been shown to increase the membrane potential, reduce ROS production, protect mitochondrial DNA, and inhibit apoptosis induction (Ahmed et al., 2008; Ale-Agha et al., 2014; Haendeler et al., 2004; Santos et al., 2004), indicating an additional protective function of telomerase in mitochondria under conditions of increased oxidative stress. A positive correlation between mitochondrial hTERT and levels of oxidative stress also has been observed in cord blood mononuclear cells of newborns (Li et al., 2014), which suggests that this oxidative stress-induced accumulation of mitochondrial hTERT may protect the mitochondrial DNA from oxidative damage during gestation.

2.3. The role of telomerase activity in regulating the immune system

2.3.1 Telomerase is up-regulated upon immune activation—The immune system comprises primarily of two interacting components: innate and adaptive immunity. The innate immune system mounts rapid but unspecific responses, whereas the adaptive immune responses take longer to develop but are highly specific, and have the capacity for long-term memory. The innate immune response is mediated mainly by monocytes, natural killer cells, dendritic cells and the complement system, and it serves as the first line of defense against environmental pathogens. T- and B-lymphocytes are crucial in the development of an adaptive immune response and are activated upon antigen-presentation and recognition via unique and highly specific T-cell receptors (TCR), in combination with activating co-stimulatory signals, such as those delivered by the surface molecule CD28 (Chou and Effros, 2013). T-cells can further differentiate into various subtypes. CD8+ T- cells are mainly cytotoxic cells, which are important for the clearance of intracellular pathogens, whereas CD4+ T-cells primarily regulate the cellular and humoral immune responses. Additionally, T-cells can be naive or antigen-experienced, and can exist in a resting or activated state (Chaplin, 2010).

Antigen activated lymphocytes express higher levels of telomerase activity. In T-cells, crosslinking of the TCR and CD28 by antigens, lectins or antibodies initiates a signal transduction cascade that ultimately induce the translocation of transcription factors such as NF-kB to the nucleus, initiating IL-2 production, entry into the cell cycle, DNA synthesis, and telomerase activation (Buchkovich and Greider, 1996; Paul and Schaefer, 2013). The up-regulation of telomerase activity facilitates the immune response and prevents immune cell senescence during fast and profound (clonal) cell expansion. However, the level of telomerase expression is not sufficient to indefinitely prevent telomere shortening and senescence (Hathcock et al., 2005).

2.3.2. Telomerase activity is reduced in senescent T-cells—A considerable body of research has focused on the role of senescent T-cells during aging and disease. Senescent T-cells lack the CD28 co-stimulatory receptor. However, also other T-cell markers, like CD27, CD57, the killer cell-lectin-like receptor G1 and programmed death receptor 1 have been associated with senescence (Dedeoglu et al., 2017; Henson et al., 2009). The proportion of CD28+ cells decreases with age and is associated with decreased responses to vaccines in the elderly, reduction in the overall T-cell receptor repertoire, and diminished control over infections (Chou and Effros, 2013). In the total PBMC population senescent CD28- T-cells have the lowest telomerase activity and shortest telomere length (Lin et al., 2010). A higher percentage of CD8+CD28- T-cells is correlated with shorter PBMC telomere length. Moreover, PBMC telomerase activity seems to decline with age (Lin et al., 2015). CD28 signaling is required for optimal telomerase up-regulation, as indicated by the paralleled loss of telomerase activity and CD28 expression in T-cells after chronic antigen stimulation *in vitro* (Valenzuela and Effros, 2002). Senescent T-cells produce reduced levels of the antiviral cytokine, interferon(IFN)-γ, and increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α (Effros, 2009). Interestingly, the loss of CD28 in a long-term stimulated CD8+ T cell culture is delayed by inhibition of TNF-α and is paralleled by increased telomerase activity (Parish et al., 2009). Prostaglandin E_2, a lipid pro-inflammatory immune mediator, inhibits hTERT transcription and telomerase activity in a long term culture of activated CD8+ T cells. This reduction in telomerase activity is associated with telomere shortening, and is accompanied by increased intracellular ROS and loss of CD28 surface expression. It also appears that the effects of prostaglandin E_2 on telomerase and CD28 expression and the progression of human CD8+ T cells towards replicative senescence are mediated by the cAMP-PKA pathway, potentially by inhibiting IL-2 signaling pathways (Chou et al., 2014). A more recent study measured T-cell telomerase activity at the single-cell level and observed a robust increase in telomerase activity in only a subset of CD28+ T-cells upon immune stimulation. Moreover, it was shown that solely the CD28+ T-cells that induced a robust telomerase response were capable of maintaining their telomere lengths during proliferation (Huang et al., 2017). The observation that telomerase can still be induced in a subset CD8+CD28- T cells, indicates that other co-stimulatory pathways may be involved in its upregulation. For example, CD8+CD28- T cells lacking the CD27 co-stimulatory receptor (CD8+CD28-CD27- T-cells) showed the shortest telomeres and extremely poor telomerase activity. The loss of telomerase up-regulation in this CD8+/CD28-/CD27- T-cell subset was associated with

defective hTERT phosphorylation by Akt, but not by reduced expression of hTERT. (Plunkett et al., 2007).

Senescence of specific T-cells might result from chronic infection by viruses such as human herpes virus, human immunodeficiency virus (HIV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Hepatitis B/C/D, human T-cell leukemia virus type 1, herpes simplex virus-1/2 and Varicella-Zoster virus (Bellon and Nicot, 2017), and several studies have examined telomerase activity in the context of virus exposure. For example, HIV-1 specific CD8+ T-cells from individuals that achieve spontaneous control of HIV-1 viremia show longer telomeres and higher levels of telomerase activity compared to virus specific CD8+ T-cells from HIV-1 progressors (Lichterfeld et al., 2008). Also, hTERT mRNA levels were lower in PBMCs of hepatitis B and C virus infected individuals, compared to healthy controls (Satra et al., 2005). Although high telomerase activity maintained telomere length in EBV-specific T-cells from individuals suffering a primary infection, later in life these specific T-cells displayed shorter telomere length and lower telomerase activity (Akbar and Vukmanovic-Stejic, 2007). Another study found that elevated CMV IgG among CMV seropositive individuals was related to lower telomerase activity, while CMV seropositivity was only associated with decreased telomerase activity among women but not men (Dowd et al., 2013). It has been shown that viruses like CMV and EBV can be reactivated during periods of chronic stress and disease, wherein the cellular immune response is impaired and virus replication can be enhanced (Rector et al., 2014). Therefore, the observation that telomerase activity is inhibited during periods of chronic stress and chronic virus exposure may be a reflection of impaired cell-mediated immunity. Chronic virus infection also induces the release of IFN-α by plasmacytoid dendritic cells, which inhibits telomerase activity by transcriptional and posttranscriptional mechanism and induces the loss of CD28 in human CD8+ T-cells *in vitro* (Lanna et al., 2013).

2.3.3. Telomerase and the regulation of immune function-related gene expression—Increasing evidence supports a regulatory role of telomerase in immune function related gene expression that is independent of telomere length. The exact mechanisms are still unknown, but several theories have been proposed. It is likely that telomerase influences gene expression by modulating chromatin structure, and/or by making epigenetic modifications via its interaction with transcription factors or chromatin modifying factors (Zhou et al., 2014). For example, hTERT interacts with transcription factors NF-KB and β-catenin, both of which are essential for proliferation and elicitation of an immune response (Akiyama et al., 2004; Ding et al., 2013; Ghosh et al., 2012; Zhou et al., 2014).

NF-KB is a key regulator of cell survival, proliferation, inflammatory responses and immune regulation. The continuous activation of the NF-KB pathway leads to chronic inflammation, which is causally linked to the development of many stress- and aging-related disorders (Miller et al., 2014). In lymphocytes, telomerase activity and the nuclear translocation of telomerase is induced by the PI3K-Akt- NF-KB signaling pathway in response to TNF-α (Akiyama et al., 2004). hTERT also regulates the expression of a subset of NF-KB-dependent genes (Ding et al., 2013; Ghosh et al., 2012). The observation that hTERT binds to the NF-KB p65 subunit and is recruited to a subset of NF-KB promoters (such as those of IL-6 and TNF-α, probably by binding to a T2G3 sequence near the NF-KB binding site) suggests that

telomerase can provide a feed forward loop for the immune system by stimulating NF-KB-dependent gene expression (Ghosh et al., 2012).

Human TERT interacts with β-catenin and can act as a cofactor in the β-catenin transcription complex (Zhou et al., 2014). Vice versa, the Wnt/β-catenin pathway can directly regulate the transcription of hTERT (Hoffmeyer et al., 2012). The Wnt/β-catenin pathway controls many processes, including organ development, cell fate decision, and stem cell renewal. Moreover, it is essential for normal T-cell development, memory CD8+ T-cell formation and persistence, and it is required for CD4+ Th2 differentiation and CD4 re-expression on a subset of CD8+ T-cells involved in antiviral immune responses (Schenkel et al., 2010; Xue and Zhao, 2012). However, the effects of hTERT on Wnt signaling might be context and cell type specific, as other studies failed to find evidence that hTERT promotes Wnt signaling in multiple breast cancer cell lines (Listerman et al., 2014). Also, hTERC, the RNA component of the telomerase holoenzyme, appears to protect against dexamethasone-induced apoptosis in CD4+ T-cells (Gazzaniga and Blackburn, 2014). Taken together, it is apparent that telomerase plays an important role in pathways underlying immune activation, differentiation and immunosenescence by exerting effects on key immunoregulatory transcription factors. Figure 1 provides a schematic overview of the regulation and regulatory functions of hTERT/telomerase in immune cells.

3. Telomerase in stress- and aging-related pathologies and conditions

Shorter leukocyte telomere length has been associated with psychological stress and also with several stress- and aging-related physical and mental disorders including cardiovascular disease (D'Mello et al., 2015; Haycock et al., 2014), type 2 diabetes (Tamura et al., 2016), autoimmune diseases (Georgin- Lavialle et al., 2010) and depression (Schutte and Malouff, 2015). Several studies on human telomerase in the context of acute and chronic stress exposure highlight the importance of stress and stress physiology as important regulators of the telomere biology system. In the following section, we first summarize findings about telomerase in the context of acute and chronic psychological stress (see also Table 1), and second, we discuss research on telomerase in the context of cardio-metabolic, autoimmune, and mental disorders (Table 2).

3.1. Stress and telomerase; differential effects of acute vs chronic stress

3.1.1. The effects of acute stress on telomerase expression—To the best of our knowledge, only two published studies to date have described the effects of acute stress on telomerase activity in humans (Table 1). The first study was conducted in a population of chronically stressed and healthy (control) women and found that PBMC telomerase activity increased by 18% after a standardized stress test (Trier Social Stress Test; TSST) across both groups. Although overall telomerase activity was influenced by blood immune cell composition, the increase in telomerase activity was independent of immune cell type. Interestingly, women responding with a higher cortisol response to the acute stress paradigm exhibited a greater increase in PBMC telomerase activity, indicating that telomerase activity may be responsive to acute changes in stress hormones (Epel et al., 2010). As discussed by these authors, telomerase activity levels may change dynamically in response to stress,

probably to protect telomeric regions or mitochondria from the effects of stress-induced acute increases in biological stress mediators such as oxidative stress. Alternatively, the increase in telomerase activity could also indicate the anticipation or preparation of the immune system to immune activation.

The second study, conducted by our research program, examined the effect of acute stress exposure on a measure of *in vitro* stimulated telomerase activity in a population of healthy young adult women and men (de Punder et al., 2018). This measure of telomerase differs from the first study in that it captures the maximal capacity of immune cells to express telomerase using a mitogen challenge across a 3-day period of time. We observed no difference in induced telomerase activity levels in PBMCs obtained before and immediately after exposure to the standardized stress test (TSST). We did, however, find an inverse correlation between total telomerase production and the cortisol response to the stress test, suggesting that individuals exhibiting higher psychophysiological stress-reactivity exhibit a reduced capacity to induce telomerase activity upon mitogen challenge. Consistent with our findings, a previous study had reported that exogenous hydrocortisone inhibited telomerase production in human stimulated T-cells (Choi et al., 2008). Glucocorticoids place a limit on the maximal activity of the immune system, modulate inflammatory gene transcription (Barnes and Adcock, 2009), and can, either through direct action or through the modulation of cytokine release, inhibit lymphocyte proliferation and immune cell activity (Bauer, 2005), to thereby influence telomerase regulatory pathways (Buchkovich and Greider, 1996; Kawauchi et al., 2005). It is likely that individuals experiencing persistently exaggerated stress responses are exposed to greater concentrations of cortisol over longer periods of time, which may have consequences on the immune- and telomere system.

3.1.2. The effects of chronic stress on the immune system and telomerase expression—Chronic psychological stress has been linked to dysregulation of the immune system, for example by altering the cytokine balance from type-1 (cytotoxic) to type-2 cytokine (humoral) driven responses. The dysregulation of the immune system is accompanied by chronic low-grade inflammation, increased oxidative stress levels, delayed wound healing, poor responses to vaccine and increased susceptibility to infectious diseases (Glaser and Kiecolt-Glaser, 2005). In addition, chronic stress has been linked to shorter telomere length (Mathur et al., 2016; Oliveira et al., 2016). This association is also observed in the context of exposure to prenatal (Entringer et al., 2018) and early life stress (Coimbra et al., 2017). The effects in humans of chronic stress on telomerase activity have been described in six published studies to date (Damjanovic et al., 2007; de Punder et al., 2018; Epel et al., 2004; Epel et al., 2010; Epel et al., 2006; Zalli et al., 2014) (Table 1). Three of these studies (Epel et al., 2004; Epel et al., 2010; Epel et al., 2006) report a suppressive effect of chronic stress on basal telomerase activity. These effects may possibly be driven by chronic stress-induced increases in oxidative stress levels (Aschbacher et al., 2013), inducing the nuclear export of hTERT to the cytosol and decreasing nuclear and total telomerase activity (Haendeler et al., 2004). In addition, ROS causes telomeres to shorten more quickly, resulting in the accumulation of senescent immune cells expressing lower levels of telomerase activity. Alternatively, prolonged periods of psychological stress might render individuals more susceptible for virus-reactivation and continuous virus-exposure, which

also induces senescence of specific T cells (Akbar and Vukmanovic-Stejic, 2007). Contrary findings were observed in a study of caretakers of patients with Alzheimer' disease and age-matched controls. Caretakers displayed shorter telomere length in parallel with higher (basal) telomerase activity, while no differences in stimulated telomerase activity and the number of CD28- T-cells were seen between caretakers and controls (Damjanovic et al., 2007). Shorter telomere length in combination with higher (basal) telomerase activity was also associated with chronic psychological stress in older men (Zalli et al., 2014). The authors of this report suggest the finding may result from a potential increase in immune cell proliferation induced by continuous stress-induced immune stimulation (chronic low-grade inflammation), thereby increasing telomerase activity, but not high enough to maintain telomere length under conditions of chronic stress. In addition, elevations in telomerase activity in combination with shorter telomere length may reflect a counter-regulatory adaptation to states or conditions like a physiological stress exposure that have the potential to reduce telomere length. Finally, we have recently reported that a 25% reduction in the capacity of immune cells to mount a telomerase activity response after challenge was observed between subjects reporting high levels of chronic stress compared to individuals that perceived medium or low levels of chronic stress (de Punder et al., 2018). The protocol used in our study particularly stimulates cell types involved in cellular immunity, the component of the immune system that is initially affected by chronic stress exposure (Segerstrom and Miller, 2004). Chronic stress has been associated with blunted mitogen-induced lymphocyte proliferation and mitogen-induced IL-2 production (Bauer et al., 2000), both activators of signaling pathways stimulating telomerase activity (Buchkovich and Greider, 1996; Kawauchi et al., 2005). In addition, chronic stress exposure is associated with a higher level of oxidative stress (Aschbacher et al., 2013), eventually resulting in the accumulation of senescent (CD28-) T cells. Senescent T cells show impaired upregulation of telomerase activity after chronic antigen stimulation (Valenzuela and Effros, 2002) and could therefore inhibit telomerase activity induction capacity.

Taken together, contradictory results have been observed on chronic stress exposure and telomerase activity, which may be indicative of the dynamic regulation of telomerase activity by different biological mechanisms, like stress hormones, inflammatory mediators and oxidative stress. Until now, most research examining telomerase activity in the context of chronic stress exposure have not systematically studied these mechanisms and therefore further experimental investigations are needed to explain and reconcile some of the inconsistencies in the literature.

3.2. Cardiometabolic diseases and telomerase

The metabolic syndrome is associated with chronic systemic low-grade inflammation, oxidative stress and vascular endothelial dysfunction (Eckel et al., 2010). While the role of telomere length in the onset and progression of cardiovascular disease has been extensively studied (D'Mello et al., 2015; Haycock et al., 2014), only a few studies have assessed telomerase activity in this context (Table 2). In the CARDIA study, higher levels of PBMC telomerase activity predicted higher prevalence of coronary artery calcium (a measure of calcified atherosclerosis), especially in individuals with shorter telomeres (Kroenke et al., 2012). In parallel with elevated plasma levels of TNF-α, IL-6, sCD163 and asymmetric

dimethyl arginine (a marker for endothelial dysfunction), PBMC telomerase activity was significantly elevated in patients with metabolic syndrome when compared to healthy volunteers. Significant negative correlations were found between telomerase activity and HDL and waist circumference, while telomerase activity was positively correlated with asymmetric dimethyl arginine. Yet, no associations were observed with TNF-α and IL-6 and telomerase activity (Rentoukas et al., 2012). Also, non-alcoholic fatty liver disease was associated with elevated hTERT mRNA expression (Laish et al., 2016). The elevated telomerase activity levels observed in patients with cardiometabolic disease could possibly be explained by a pro-inflammatory state, producing a feed-forward loop between NF-KB and hTERT (Ghosh et al., 2012). An alternative explanation could be that leptin, an adipokine important for energy homeostasis and associated with cardiometabolic risk factors (Ingelsson et al., 2008), induces expression of hTERT via STAT3 (Sundin and Hentosh, 2012). Finally, elevations in telomerase activity may reflect a counterregulatory adaptation to physiological stressors that reduce telomere length (Beery et al., 2012; Zalli et al., 2014).

3.3. Autoimmune disease and telomerase

During aging, the ability of the immune system to differentiate between pathogens and normal tissues diminishes, and the risk for immune responses against “self” body tissues increases. For example, autoantibody production increases with age, which in elderly individuals is inversely correlated with a decreased proliferation of T-cells in response to a mitogen challenge (Agarwal and Busse, 2010).

Most studies investigating telomerase in autoimmune diseases have found increased telomerase activity or hTERT gene expression in disease versus healthy states (Katayama and Kohriyama, 2001; Kurosaka et al., 2001; Kurosaka et al., 2003; Kurosaka et al., 2006; Qi et al., 2013; Tarhan et al., 2008; Wu et al., 2000; Wu et al., 1999a; Yudoh et al., 1999). However, one study observed no difference (Vazirpanah et al., 2017) and two studies reported lower hTERT mRNA expression in patients compared to healthy controls (Tarhan et al., 2008; Zhang et al., 2016). Interestingly, differences in telomerase activity were observed between active and inactive disease (Katayama and Kohriyama, 2001), probably due to changes in inflammatory and oxidative stress levels. Furthermore, differences in telomerase activity between early-and advanced-stage disease (Invernizzi et al., 2014) indicate that telomerase activity may fluctuate across the course of a disease (Table 2). A few studies assessing telomerase activity or hTERT expression following mitogen stimulation *in vitro* observed either a reduced capacity to induce telomerase activity (or hTERT expression) (Fritsch et al., 2006; Fujii et al., 2009; Thewissen et al., 2005) in patients, or observed no differences between the different disease- and control groups (Wu et al., 1999a) (Table 2). Immune dysregulations in combination with a reduced capacity to induce telomerase activity in response to challenge might explain accelerated telomere attrition rates observed in these pathologies.

3.4. Mental diseases and telomerase

Studies on the association of basal PBMC telomerase and mental disorders such as depression, posttraumatic stress disorder (PTSD) and schizophrenia have produced heterogeneous results (Chen et al., 2014; Jergovic et al., 2014; Porton et al., 2008; Simon et

al., 2015; Wolkowitz et al., 2012) (Table 2). In the context of depression, a study of medication-free depressed individuals and healthy controls found that PBMC telomerase activity levels were elevated in depressed individuals compared to controls and were directly correlated with symptom severity (Wolkowitz et al., 2012). Also, higher PBMC telomerase activity was observed in depressed males versus controls, however, this association was not observed in women (Simon et al., 2015). Furthermore, in depressed patients, exposure to adverse childhood experiences (ACE) was associated with increased PBMC telomerase activity and a higher telomerase: telomere length ratio, while in healthy controls ACE exposure was associated with shorter telomeres and not associated with telomerase activity (Chen et al., 2014).

PBMCs from PTSD patients compared to those of healthy controls displayed shorter telomeres but comparable telomerase activity levels and *in vitro* immune responses. Yet, elderly participants with PTSD in the same study had shorter telomere length and lower telomerase activity levels, paralleled by increased *in vitro* (spontaneous) pro-inflammatory cytokine production (IL-6 and TNFα) and reduced T-cell proliferation (Jergovic et al., 2014). These findings may possibly be explained by the increased presence of senescent immune cells in the elderly population. Compared to healthy individuals, schizophrenia patients showed decreased PBMC telomerase activity levels that were accompanied by shorter telomeres (Porton et al., 2008). The precise mechanisms underlying the observed differences in PBMC telomerase activity between the abovementioned studies remain to be elucidated, but may be indicative of the dynamic regulation of telomerase activity in different stress- and disease states.

Finally, the ratio between PBMC telomerase activity and telomere length was associated with age-related structural brain changes in healthy adults, suggesting that changes in telomere biology can also reflect age-related structural brain alterations (Jacobs et al., 2014).

4. Lifestyle interventions targeting telomerase

Based on the consideration that the adverse effects of stress on the telomere system may be mediated, in part, via unhealthy behaviors that are associated with stress exposure (e.g., more sedentary behavior, unhealthy diet, smoking, substance abuse), it has been suggested and demonstrated in several studies that a healthy lifestyle with respect to nutrition, stress management and exercise may promote longer telomeres (Ornish et al., 2013; Puterman et al., 2013). This effect has been attributed to changes in telomerase activity (Boccardi et al., 2013; Ornish et al., 2008). Because intervention studies, in contrast to cross-sectional studies, provide stronger evidence for a causal role of stress-related processes on telomerase activity, we have reviewed here only those studies that have performed an intervention, but not those that have merely reported correlations. The effects of different lifestyle interventions on telomerase activity and or expression are summarized in Table 3.

4.1. Lifestyle and diet/nutrition interventions

A three-months intensive lifestyle change intervention that included modifications in diet, exercise and stress management in men diagnosed with low-risk prostate cancer was found to increase PBMC telomerase activity (Ornish et al., 2008). However, no changes in

telomerase activity were observed between controls and a small group of men that continued these changes over a 5 year period. Nevertheless, after 5 years, telomere length increased in the intervention group, while it declined in the control group (Ornish et al., 2013). Twelve weeks of supplementation with an antioxidant formula increased telomerase activity in healthy women. The supplement also improved vitamin D deficiencies, reduced oxidative stress, and increased the antioxidant potential (Balcerczyk et al., 2014). In schizophrenia patients, higher PBMC telomerase activity was observed after 26 weeks of n-3 PUFA (fish oil) supplementation added to antipsychotics compared to adding a placebo. Increases in telomerase activity were associated with improvements in depressive symptoms and disease severity (Pawelczyk et al., 2018). Higher serum vitamin D3 levels have been shown to be associated with longer telomere length in women (Richards et al., 2007). The effect of 16 weeks of vitamin D3 (60,000 IU/month) supplementation on telomerase activity was investigated in a randomized, double-blind, placebo-controlled clinical trial with overweight African American women (Zhu et al., 2012). In the vitamin D3 group PBMC telomerase activity increased by 19.2% from baseline, while in the control group no effect was observed. Vitamin D3 and N-3 PUFA are known to have immune modulatory effects (Calder, 2015; Kamen and Tangpricha, 2010) and can shape epigenetic changes in pathways involved in telomerase regulation (Lu et al., 2018; Tremblay et al., 2017). However, the exact mechanism underlying the upregulation of telomerase activity after Vitamin D3 and n-3 PUFA supplementation remains to be elucidated.

4.2. Exercise

Habitual physical exercise is associated with longer telomere length (Cherkas et al., 2008). Acute exercise up-regulated PBMC hTERT mRNA expression in healthy volunteers (Chilton et al., 2014). Similarly, a single session of treadmill running resulted in an acute increase in PBMC telomerase activity in healthy young individuals, again indicating the dynamic responses of telomerase to acute stimuli. Five weeks of regular individual shear rate therapy in elderly suffering from peripheral artery disease also increased post-assessment telomerase activity levels (Zietzer et al., 2016).

4.3. Meditation

The perception of and coping with stress can be altered by meditative practice. Most intervention studies examining the effect of meditation on telomerase activity observed elevations in PBMC telomerase activity or telomerase gene expression after an intervention period (Daubenmier et al., 2012; Duraimani et al., 2015; Epel et al., 2016; Ho et al., 2012; Jacobs et al., 2011; Lavretsky et al., 2013; Lengacher et al., 2014; Tolahunase et al., 2017; Tolahunase et al., 2018). A more recent study observed an increase in PBMC telomere length, but no difference in telomerase activity, in participants of a meditation retreat compared to non-participating controls. Interestingly, pre-assessment telomerase activity levels were associated with greater telomere length increases across both groups, while postassessment telomerase levels were negatively correlated with reports of practice diligence and the number of hours of practice time during the retreat (Conklin et al., 2018). Pre-assessment telomerase activity was also lower in regular meditators compared to non-meditators, but tended to increase only in the regular meditation group (Epel et al., 2016). It is not clear how practicing meditation increases telomerase activity, but a plausible

mechanism is that decreases in psychological stress levels through regular meditative practice are associated with lower stress-related endocrine, immune and oxidative parameters.

Accumulating endogenous oxidative stress induces the nuclear export of hTERT to the cytosol and decreases nuclear and total telomerase activity (Haendeler et al., 2004). It could be possible that meditative practice and other positive life-style interventions reverse this process.

5. Methodological considerations in the assessment of telomerase

5.1. Baseline versus stimulated telomerase activity

Telomerase can be measured under several conditions. To date, most human studies have investigated telomerase activity in PBMCs isolated from whole blood and have measured *basal* telomerase activity in the total cell fraction or in different immune cell populations. However, we suggest that the interpretation of such data poses various challenges for the following reasons: Firstly, telomerase levels are normally expressed at very low levels in resting PBMCs, making it possible that expression can be missed or misinterpreted if it is below or close to the assay's lower limit of detection. Secondly, telomerase levels may vary as a function of cell-cycle stage and other biological factors such as inflammatory mediators, stress hormones and oxidative stress. Thirdly, differences in telomerase levels may also reflect the secondary (counter-regulatory) adaptations to states and conditions that reduce telomere length (Zalli et al., 2014). Higher telomerase activity levels can be induced upon antigenic/mitogenic stimulation. Therefore, in some studies, immune cells were cultured and stimulated *in vitro* with an antigen or mitogen to induce maximal telomerase production (Choi et al., 2008; Damjanovic et al., 2007; Fritsch et al., 2006; Son et al., 2000; Thewissen et al., 2005). The potential advantage of this approach is that it may bypass the above-mentioned limitations to provide an indicator of individual differences of the overall capacity of immune cells to respond to an ecologically relevant challenge. For example, it has been shown in CD4+ T-cells that the level of telomerase activity induced by *in vitro* stimulation was correlated with changes in telomere length, while no decrease in the stimulated level of telomerase activity was observed with age (Son et al., 2000). However, contrasting findings have shown that stimulated T-cell (both CD8+ and CD4+) telomerase activity declines with age (Lin et al., 2015).

This discrepancy could possibly be explained by dissimilarities in the stimulation protocols and subsets of immune cells across these studies. We have recently advanced the use of an *in vitro* measure of maximal telomerase activity capacity (mTAC) of human PBMCs to a mitogen challenge (PHA+IL-2). We have determined that this measure empirically meets the criteria to represent a potentially useful individual difference construct, with adequate within-subject stability and between-subject variability. We have reported that mTAC does not appear to be influenced by situational factors including time of day, acute stress exposure, and immune cell distribution in the pre-stimulation blood sample. The mTAC measure is, however, associated with key stress-related states and traits, including perceived chronic stress and psychophysiological stress responsivity (de Punder et al., 2018). Based on the findings and considerations discussed above, we have advanced the concept that studies

of the capacity of immune cells to mount a telomerase response to challenge may represent a useful individual difference measure, either independently or in combination with measures of basal telomerase activity and telomere length.

5.2. Immune cell distribution

Telomerase activity is known to vary by immune cell subtype. Biological factors such as stress hormones and inflammatory mediators and the circadian rhythm alter the trafficking of immune cells in and out of the circulation, thereby potentially influencing telomerase activity levels in isolated PBMCs. Early studies on telomerase expression in different subtypes of isolated immune cells reported detectable levels of telomerase activity in all T and B cell fractions, but undetectable levels in the monocytic fractions (Bodnar et al., 1996). Later findings in four lymphocyte subpopulation have suggested that senescent CD28- T-cells display the lowest telomerase activity, while B-cells have the highest telomerase activity, and that CD4+ T cells exhibit slightly higher telomerase activity than CD8+CD28+ T cells (Lin et al., 2010). However, it appears that within-individual telomerase activity across all four cell types is correlated, indicating that telomerase activity in these lymphocyte subpopulations may be regulated by common pathways (Lin et al., 2010). In whole blood, greater percentages of monocytes were associated with higher telomerase activity levels, while higher percentages of CD8+ T-cells were related to lower levels of telomerase activity (Epel et al., 2010). Our own study did not find significant alterations in stimulated telomerase activity (mTAC) as a function of immune cell type distributions present before *in vitro* stimulation. However, only the whole fraction of CD8+ cells was studied here, and no distinction was made between naïve, effector and memory CD8+ T-cells, or CD8+ CD28- T-cells. The percentage of senescent cells could influence mTAC, as it has been shown that CD28 signaling is required for optimal telomerase upregulation (Valenzuela and Effros, 2002),

5.3. Measurement of telomerase activity

Telomerase activity can be measured by a highly sensitive PCR-based method -- the telomerase repeat amplification protocol (TRAP) -- which was originally designed to measure telomerase in cancer cells (Counter et al., 1992; Kim and Wu, 1997; Morin, 1989). In this assay, endogenous telomerase adds a number of telomeric repeats on to the 3’ end of a substrate oligonucleotide. The products of telomerase-mediated extension of the substrate oligonucleotide are then amplified by PCR using reverse primers. This generates a ladder of bands with 6 base increments (the size of the telomeric repeat). In the first protocol a radioactive-labeled substrate oligonucleotide was used that could be detected by polyacrylamide electrophoresis followed by autoradiography. Later, fluorescein-labeled substrate primers or just a simple conventional in-gel staining of the products were used for detection. The use of energy transfer primers makes it possible to detect telomerase activity directly from reaction kinetics with real-time PCR. In addition, a very sensitive PCR ELISA kit is commercially available that combines a biotinylated substrate primer with a microplate detection format (extensively reviewed by Fajkus, 2006 (Fajkus, 2006)). When performing the TRAP assay it should be noted that isolating PBMCs from whole blood may result in different amounts of contaminating red blood cells and platelets, which may contribute to total protein in the extract. Therefore, more recent studies use viable cell numbers to

normalize among different samples, instead of normalizing to total protein (Lin et al., 2010). Finally, a novel PCR technology, droplet digital PCR (ddPCR), has made it possible to quantify telomerase enzyme activity on a single-cell basis (ddTRAP) technique (Ludlow et al., 2014).

6. Conclusions and implication for further research

As reviewed above, telomerase is highly regulated in response to various biological factors and systems, such as stress hormones, inflammatory mediators, oxidative stress and the circadian rhythm. Therefore, we suggest that future studies of PBMC telomerase should include measures of these processes/biomarkers and should standardize potential confounding factors such as time of day of blood collection. Moreover, because, telomerase activity can vary by immune cell subtype, when characterizing total PBMC telomerase under conditions of stress and/or presence of disease states, it may be important to also assess possible changes in the distribution of various immune cell subpopulations, including senescent immune cells.

To date, basal telomerase activity has not been found to be associated with telomere length when measured in total PBMC. This might be explained by the possibility that changes in telomerase are only related to telomere length in a subset of the total PBMC population and are therefore not revealed in total PBMC measurements. Also, it is important to note that changes in telomerase could be related to only a subset of the total PBMC population and could be independent of telomere length. Thus, future studies including telomerase and telomere length measurements on the single cell level are clearly warranted to fill in these research gaps. Future studies should also consider the telomere-independent functions of telomerase, for example, its role in protecting mitochondria against oxidative stress, to gain a broader knowledge of the role of telomerase in health and stress-related disease risk. Moreover, longitudinal studies on telomerase activity and change in telomere length are warranted. Only a relatively small number of studies have investigated the characteristics of stimulated telomerase responses. A reduced capacity for induction of telomerase might explain why telomeres shorten faster under pathological conditions. As reviewed above, stimulated telomerase activity levels and hTERT mRNA expression levels are reduced in several disease states (Fritsch et al., 2006; Fujii et al., 2009; Thewissen et al., 2005), associated with stress-related states and traits, and appear to be independent of situational factors such as acute stress exposure and time of day of blood collection (de Punder et al., 2018). For these reasons, the characterization of individual differences in the capacity of the telomere biology system to respond to challenge, in addition to measures of basal telomerase activity and telomere length, may represent a promising approach in future studies of telomere biology and stress- and aging-related disease risk.

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Highlights

- Telomerase preserves healthy cell function and influences immune function-related gene expression.
- Stress and stress physiology are important regulators of telomerase.
- The telomerase response to challenge may represent a useful individual difference measure.

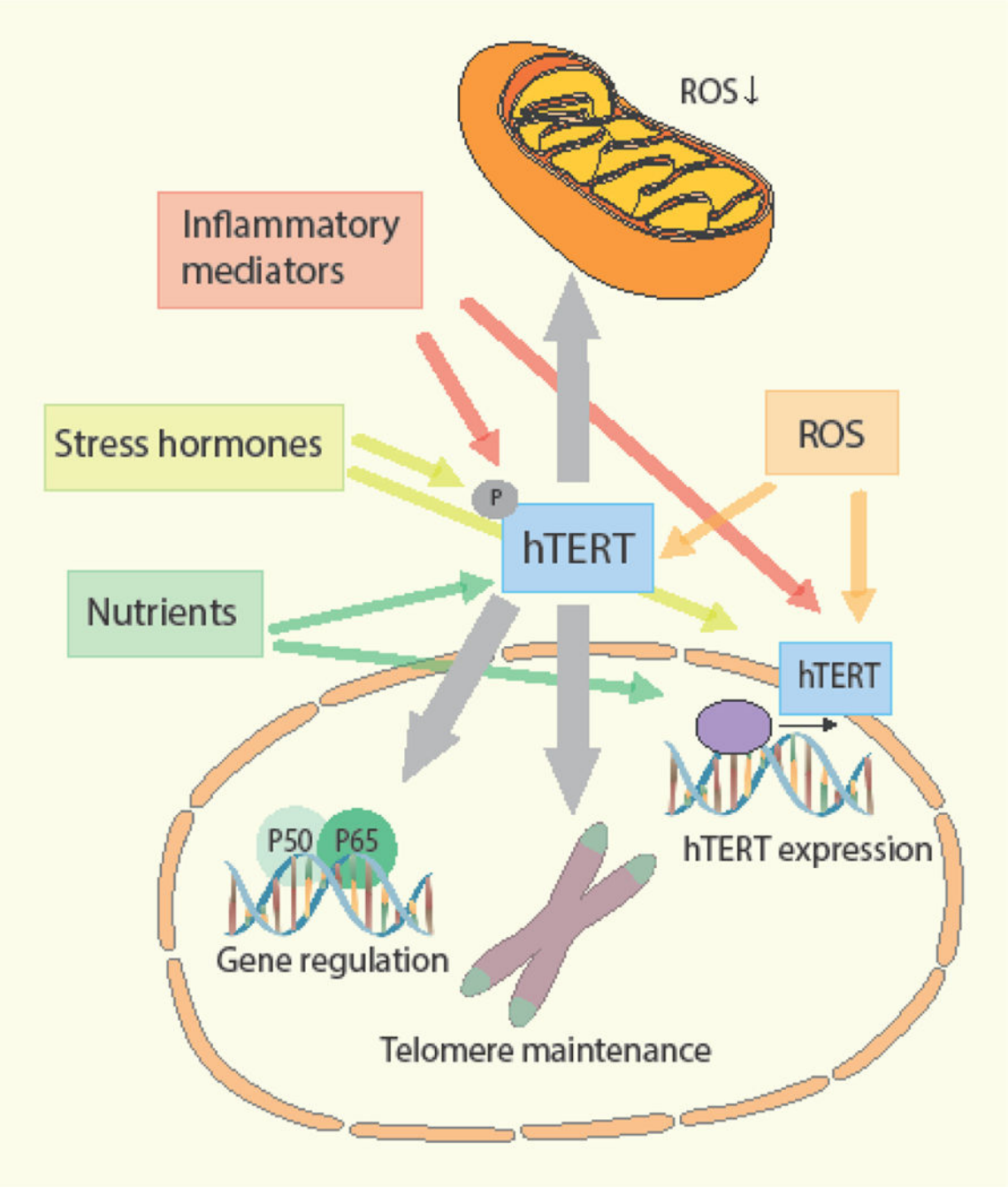

Figure 1.
Overview of the regulation and regulatory functions of hTERT/telomerase in immune cells. Telomerase protects mitochondria against oxidative stress, regulates immune-related gene expression and maintains telomere length during immune activation. Inflammatory mediators, stress hormones, nutrients and ROS all influence telomerase expression, telomerase activity and its cellular localization by epigenetic, translational and posttranslational (e.g. phosphorylation) machanisms. ROS, Reactive oxygen species.

Table 1.

Human studies on stress and PBMC telomerase.

Ref	Study design	Predictor	Basal TA	Stimulated TA	Effects
(Epel et al.,2004)	39 healthy caregiving mothers, 19 controls	Chronic stress	TA ↓		Mean TA 48% lower in high-stress group. The group with short TL showed higher perceived stress levels and displayed higher oxidative stress and lower TA levels.
(Epel et al., 2006)	62 healthy mothers	Chronic stress	TA ↓		Lower TA associated with higher stress arousal, perceived stress and chronicity of stress. Lower TA associated with several risk factors for cardiovascular diseases.
(Damjanovic et al., 2007)	41 Alzheimer caregivers, 41 controls	Chronic stress	TA ↑	No difference	Caregivers showed higher TA and shorter TL. Similar results in isolated T-cells. No difference in stimulated TA. Caregivers showed reduced stimulated proliferation and increased cytokine production of T cells.
(Epel et al., 2010)	44 postmenopausal women: 22 caretakers, 22 controls	Chronic stress Acute stress	TA ↓ TA ↑		Caretakers lower TA activity at baseline. 18% higher TA in response to TSST in both groups. TA response higher in persons responding with higher cortisol. TA activity was associated with threat appraisal in controls.
(Zalli et al., 2014)	333 middle aged and elderly healthy men and women	Stress reactivity	TL ↓ + TA ↑		Males with shorter TL and high TA showed blunted stress-reactivity compared to men with longer TL or men with shorter TL and low TA.
		Stress recovery	TL ↓ + TA ↑		Males with shorter TL and high TA showed reduced post-stress recovery. Shorter TL in combination with high TA was associated with reduced social support, lower optimism, higher hostility, and greater early life adversity.
(de Punder etal., 2018)	28 healthy participants	Acute stress		No difference	No difference in stimulated TA levels before and after TSST exposure.
		Stress-reactivity		TA ↓	Inverse correlation between overall TA levels and the cortisol response.
		Chronic stress		TA ↓	Individuals exposed to high levels of chronic stress showed a 25% reduction in induced TA levels compared to individuals perceiving medium or low levels of stress.

Abbreviations: BP, blood pressure; TA, telomerase activity; TL, telomere length; TSST, Trier Social Stress Test.

Table 2.

Human studies on PBMC telomerase in disease.

Ref	Study design	Predictor	Basal TA	Stimulated TA	Effects
Cardio-metabolic disease					
(Rentoukas etal., 2012)	39 patients with metabolic syndrome, 20 controls	Metabolic syndrome	TA ↑		Higher TA, Il-6, TNF-α, ADMA and CD163 in patients compared to controls. Negative correlations between TA and HDL and waist circumference.
(Kroenke etal., 2012)	440 black and white men	Atherosclerosis/Coronary artery calcification	TA ↑		CRP and current smoking positively associated with TA. Low socioeconomic status associated with higher TA only in black men. TA positively associated with prevalent (15 years after follow up) and progressive (20 years after follow up) coronary artery calcification. Progression greater in individuals with short TL.
(Laish et al.,2016)	22 NAFLD patients, 20 patients with cryptogenic cirrhosis, 20 healthy age-matched controls	NAFLD Cryptogenic cirrhosis	hTERT ↑ No difference		Higher hTERT mRNA expression in NAFLD patients compared to patients with cryptogenic cirrhosis.
Autoimmune disease					
(Wu et al., 1999a)	15 atopic dermatitis patients, 13 healthy controls	Atopic dermatitis	TA ↑	No difference	Higher TA in unstimulated PBMC after 72 hours in vitro. No difference in stimulated TA after 72 hours between patients and controls. The relative increase in TA was lower in patients compared to controls.
(Yudoh et al., 1999)	18 RA patients, 9 PVS patients, 12 osteoarthritis patients, 10 controls with knee joint trauma	RA	TA ↑		Higher TA levels in RA patients compared to the other groups
(Wu et al., 2000)	16 psoriasis and 32 atopic dermatitis patients, 30 controls	Psoriasis Atopic dermatitis	TA ↑		TA increased in both patients groups compared to controls.
(Katayama and Kohriyama, 2001)	9 Sc patients, 17 SLE patients, 11 MCTD patients, 11 Sj patients	Sc SLE MCTD Sj	No difference TA ↑ TA ↑ TA ↑		No difference between Sc patients and controls TA higher in SLE, MCTD, and Sj patients compared to controls. Correlation between SLE disease activity index scores and TA.
(Kurosaka et al., 2003)	55 SLE patients, 45 controls	SLE	TA ↑		Higher TA in Sj patients with extraglandular manifestations. Higher TA in SLE patients with active disease. No difference in TA between inactive SLE patients in their 20s, 30s and 40s, but higher TA in inactive SLE patients in their 50s compared to controls.
(Thewissen et al., 2005)	15 RA patients, 8 healthy controls, 7 MS patients, 8 flu patients	Early RA, MS and Flu patients		hTERT ↓	Increase in TA related to increase in hTERT mRNA expression.

Ref	Study design	Predictor	Basal TA	Stimulated TA	Effects
					PBMCs of early-untreated RA patients, MS patients and flu patients showed reduced hTERT mRNA levels after in vitro stimulation compared to controls and chronically treated RA patients. No decrease in stimulated hTERT mRNA level observed with age.
(Fritsch et al., 2006)	37 SLE patients, 42 healthy controls	SLE		TA ↓	Stimulated TA lower in naive CD4+ and CCR7+/ CD27+ memory T cells from patients compared to controls.
(Kurosaka et al., 2006)	34 SLE patients (18 active disease, 16 inactive disease), 17 controls	SLE	TA ↓		TA in T-cells higher in both active and inactive SLE patients compared to controls. TA in B-cells higher in active SLE patients compared to controls.
(Tarhan et al., 2008)	19 Sc 15 SLE, 10 RA and 14 Sj patients, 29	RA Sc SLE Sj	hTERT ↑ hTERT ↓ No difference No difference		hTERT mRNA higher in RA group compared to controls. In RA group hTERT mRNA levels higher in clinically active healthy controls compared to non-active group. Sc patients displayed lower hTERT mRNA compared to controls.
(Fujii et al., 2009)	69 RA patients, 60 healthy age-matched controls	RA		TA ↓	Impaired induction of TA in stimulated naive CD4+ T-cells from RA patients compared to controls. No difference in memory T-cells.
(Qi et al., 2013)	37 active chronic immune thrombocytopenia patients, 22 healthy controls	Immune thrombocytopenia	TA ↑		TA increased in CD4+, CD8+ and CD19+ lymphocytes from patients compared to controls.
(Invernizzi et al., 2014)	30 women with primary biliary cirrhosis, 12 healthy women	primary biliary cirrhosis	TA ↑/TA ↓		Patients with advanced disease less TA compared to those with early-stage disease
(Zhang et al., 2016)	30 oral lichen planus patients, 19 controls	Oral lichen planus	hTERT ↓		Lower hTERT mRNA levels in CD4+ T cells of patients compared to controls. No difference in CD8+ T cells.
(Vazirpanah et al., 2017)	64 gout patients, 89 controls	Gout	No difference		No difference in hTERT mRNA levels between patients and controls.
Mental disorders					
(Porton et al., 2008)	53 schizophrenia patients, 31 unaffected relatives, 59 unrelated controls	Schizophrenia	TA ↓		Lower TA in individuals with schizophrenia compared to unaffected individuals.
(Wolkowitz et al., 2012)	20 unmedicated depressed individuals, 18 controls	MDD	TA ↑		TA elevated in depressed versus controls. TA positively correlated with inventory of depressive symptomatology and perceived stress scale ratings. Depressed group: individuals with lower pretreatment TA + greater increase in TA during treatment showed better antidepressant responses.

Ref	Study design	Predictor	Basal TA	Stimulated TA	Effects
(Chen et al., 2014)	20 unmedicated depressed adults, 20 controls	MDD + ACE exposure ACE exposure	TA ↑ No difference		In the depressed group higher ACE exposure was associated with higher TA and a higher TA: TL ratio. In healthy controls ACE exposure was associated with shorter TL, but not associated with TA.
(Jergovic et al., 2014)	30 PTSD patients (middle-aged), 17 age-matched controls, 15 elderly controls 15 elderly controls	PTSD Age	No difference TA ↓		No difference in TA between PTSD patients and controls. Elderly group showed lower TA, increased spontaneous pro-inflammatory cytokine production and reduced T-cell proliferation compared to PTSD and control group.
(Jacobs et al., 2014)	47 midlife women, including 19 with apolipoprtotein E-ε4 genotype (risk factor for accelerated aging)	Hippocampal volume	TA/TL↑		A higher TA/TL ratio was associated with lower hippocampal volume.
(Simon et al., 2015)	166 individuals with MDD,166 age- and gender-matched controls	MDD (males) MDD (females)	TA ↑ No difference		TA higher in depressed males versus controls. No difference in women.

Abbreviations: ACE, adverse childhood experiences; ADMA, asymmetric dimethylarginine; HDL, high density lipoprotein; MCTD, mixed connective tissue disease; MDD, major depressive disorder; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; PTSD, posttraumatic stress syndrome; PVS, pigmented villonodular synovitis; RA, rheumatoid arthritis; Sc, systemic sclerosis; Sj, Sjögren's syndrome; SLE, systemic lupus erythematodes; TA, telomerase activity; TL, telomere length.

Table 3.

Human intervention studies on lifestyle/meditation and PBMC telomerase.

Ref	Study design	Predictor	Basal TA	Effects
Lifestyle, diet and nutrition supplementation				
(Omish et al., 2008)	24 men with biopsy-diagnosed low-risk prostate cancer	Lifestyle changes, 3 months	TA ↑	TA increased almost 30% during the course of the 3 months intervention. Increases in TA associated with decreases in LDL cholesterol and psychological distress.
(Zhu et al., 2012)	37 overweight African Americans (18 placebo, 19 vitamin D3)	Vitamin D3 2000 IU/day oral, 16 weeks	TA ↑	TA increased by 19.2% from baseline in the vitamin D3 group. No difference in TA in the placebo group.
(Omish et al., 2013)	10 men with biopsy-diagnosed low-risk prostate cancer, 25 controls	Lifestyle changes, 5 years	No difference	No association with lifestyle changes and TA.
(Balcerczyk et al., 2014)	66 healthy women	Supplementation with an antioxidant formula, 12 weeks	TA ↑	TA increased after 12-weeks of supplementation, paralleled by increases in vitamin D level, reductions in oxidative stress levels and increases in the antioxidant potential.
(Pawelczyk et al., 2018)	71 schizophrenia patients	2.2g/day of n-3 PUFA or olive oil placebo, 26 weeks	TA ↑	Higher increases in TA in the intervention group compared to placebo group. Changes in TA were inversely correlated with improvement in depressive symptoms and severity of the illness.
Exercise				
(Chilton et al., 2014).	22 healthy males	30 minutes of treadmill running at 80% of peak oxygen uptake	hTERT ↑	hTERT mRNA expression significantly increased from pre- to 60 min post-exercise.
(Zietzer et al., 2016)	26 young healthy participants 14 elderly peripheral artery disease patients	Single session of treadmill running, 30 hrs individual shear rate therapy (ISRT) for 5 weeks	TA ↑ TA ↑	TA increased after a single bout of aerobic exercise. TA increased after a 5-week period of ISRT therapy in elderly patients suffering from peripheral artery disease.
Meditation				
(Jacobs et al., 2011)	32 healthy subjects (17 intervention, 25 waitlist controls)	Meditation retreat, 3 months	TA↑	TA activity was significantly higher in intervention group compared to control group, no baseline measured.
(Daubenmier et al., 2012)	47 overweight/obese women (24 intervention, 23 waitlist controls)	Mindfulness intervention on stress-eating, 4 months	TA ↑	18% higher TA increase in intervention group. Changes in TA were negatively correlated to changes in chronic stress, anxiety, dietary restraint, fat intake, cortisol and glucose.
(Ho et al., 2012)	64 chronic fatigue syndrome patients (33 intervention, 31 waitlist controls)	Qigong exercise, 12 weeks	TA ↑	TA increased in the intervention group. TA was higher in the intervention group compared to controls after 4 months.
(Lavretsky et al., 2013)	39 dementia caregivers with mild depressive symptoms	Kirtan Kriya meditation (n = 23) or relaxation music (n = 16), 12 min per day for 8 weeks	TA ↑	TA increased with 43.3% in the meditation group, compared to 3.7% in the relaxation group. Meditation group: correlation between TA and improved mental health score.

Ref	Study design	Predictor	Basal TA	Effects
(Lengacher et al., 2014)	142 breast cancer survivors (74 intervention, 68 waitlist controls)	Mindfulness-based stress reduction (MBSR), 6 weeks	TA↑	TA increased with 17% over 12 weeks in the MBSR group. No increase in the control group. No difference in TL between both groups.
(Duraimani et al., 2015)	48 hypertensive men and women	Transcendental Meditation + basic health education course (n = 24) or, Extensive health education program (n = 24), 16 weeks	hTERT ↑ hTERC ↑	Both groups showed increased hTERC and hTERT mRNA levels No differences between both groups.
(Epel et al., 2016)	64 non-meditating women, 30 regular meditators	Vacation or meditation retreat, 1 week	TA↑	Baseline TA lower in regular meditators TA increased only in the regular meditation group
(Tolahunase et al., 2017)	96 men and women	Yoga- and meditation-based lifestyle intervention program, 12 weeks	TA↑	TA increased, while levels of 8-OH2dG, ROS, cortisol, and IL-6 decreased after intervention.
(Tolahunase et al., 2018)	58 depressed patients (29 intervention, 29 controls)	Yoga- and meditation-based lifestyle intervention program, 12 weeks	TA ↑	TA increased, while depression severity decreased in intervention compared to control group. In addition, the intervention increased DHEAS and Sirtuin 1 levels, decreased cortisol, IL-6 and DNA damage and balanced oxidative stress.
(Conklin et al., 2018)	28 retreat participants, 34 non-participating controls	Meditation retreat, 3 weeks	No difference	No difference in TA between retreat participants and control group. Pre-assessment TA levels were associated with greater TL increases across both groups. Post-assessment TA levels were negatively correlated with reports of practice diligence and the number of hours of practice time during the retreat.

Abbreviations: DHEAS, Dehydroepiandrosteron sulfate; EEE, exercise energy expenditure; LDL, low-density lipoprotein; 8-OH2dG, 8-Oxo-2'-deoxyguanosine; PUFA, polyunsaturated fatty acid; ROS, Reactive oxygen species; TA, telomerase activity; TL, telomere length.