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Psychological Stress and Cellular Aging

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Summary and Keywords

Stress is a multistage process during which an organism perceives, interprets, and responds to threatening environmental stimuli. Physiological activity in the nervous, endocrine, and immune systems mediates the biological stress response. Although the stress response is adaptive in the short term, exposure to severe or chronic stressors dysregulates these biological systems, promoting maladaptive physiology and an accelerated aging phenotype, including aging on the cellular level. Two structures implicated in this process of stress and cellular aging are telomeres, whose length progressively decreases with age, and mitochondria, whose respiratory activity becomes increasingly inefficient with advanced age. Stress in its various forms is suggested to influence the maintenance and stability of these structures throughout life. Elucidating the interrelated connection between telomeres and mitochondria and how different types of stressors are influencing these structures to drive the aging process is of great interest. A better understanding of this subject can inform clinical treatments and intervention efforts to reduce (or even reverse) the damaging effects of stress on the aging process.

Keywords: stress, aging, telomere, mitochondria, oxidative stress, cell biology

What Is Stress?

Stress permeates society. In school, the workplace, and everyday life, humans experience the burden of stress. The conditions of modern civilization have made the title of Hans Selye's seminal work *The Stress of Life* a basic truism (Selye, 1956). This article opens by conceptualizing stress, continues with a review of biological theories of aging, and concludes by elaborating on the close relationship between these two concepts, integrating stress with aging at the cellular level.

Stress, as a concept, eludes easy definition. Part of this lies in the variety of ideas attributed to the word *stress*, which spans academia. In physics, *stress* represents the force that particles exert on each other in response to an outside influence. In chemistry, *stress* describes the force applied to a system that shifts the concentration, temperature, or pressure away from equilibrium. In biology, *stress* is a disruption to homeostasis, the delicate equilibrium maintained by physiological systems within an organism, such as body temperature or blood pH level. Although these fields are distinct, their definitions of this term share consistencies. Stress involves a perturbation of equilibrium, forcing various systems to adjust. The biopsychosocial definition of stress similarly captures this dimension. Hence, *stress* is a multistage process by which an organism perceives and interprets threatening stimuli in the environment, resulting in a stress response and adaptation to restore homeostasis.

Interpreting a stimulus is an inherently psychological process, subject to individual differences in perception, appraisal, and experience, as well as biology. Is the stimulus innocuous or is it a threat that warrants a response? The response stage of stress is partly psychological, but it includes physiological and behavioral components as well. For example, consider final exams—a near-universal stressor for students. Some ruminate over thoughts of failing (psychological), others lose sleep while studying (behavioral), and nearly all of them experience a rapid heartbeat as they take their seat and anticipate the exam being distributed (physiological). In the short term, stress is an adaptive process. The rapid heartbeat experienced by students allows them to focus on the task at hand, and ultimately perform better. While the psychological and behavioral responses to stress may differ among individuals, the systemic physiological response is essentially the same.

This physiological response is initiated along two axes of the neuroendocrine system: the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA). Each axis is activated on a different time scale and for a different purpose. Initiated first is the fast response along the SAM axis, which assists an organism’s ability to detect threats and is traditionally associated with the fight or flight response. This axis culminates with the release of epinephrine and norepinephrine from the adrenal medulla and is associated with increased blood pressure and heart rate, alertness, and muscle stimulation. The response along the HPA axis occurs more slowly and concludes with the release of glucocorticoids from the adrenal cortex. In humans, this glucocorticoid is cortisol, whose systemic effects include increasing cellular metabolism to provide the energy needed to respond to a threat. Cortisol also suppresses the activity of the immune system and terminates the stress response via a negative feedback loop.

Stress is an adaptive process, and the biological pathways are conserved across species, from worms to fish to humans. Understanding *why* stress is useful requires developing the idea through a life-history lens. Life history theory is an approach used in evolutionary developmental biology to understand an organism’s biology and behavior as shaped by natural selection. Chronic stress accelerates cellular aging and increases the risk of age-associated disease (Shalev, Entringer, et al., 2013). Life history theory, then, asks why such a process would have evolved biologically, and the answer is that stress-

induced physiological changes represent an adaptive trade-off between immediate and long-term survival. A prime example is the effects of cortisol during acute versus chronic stress. Cortisol helps to mobilize the energy needed to respond to an acute stressor and promotes a return to equilibrium once the stressor subsides, a process called *allostasis*, which is crucial for survival in the short term. However, chronic release of cortisol increases allostatic load, which is generated from repeated allostatic responses (Picard, Juster, & McEwen, 2014), eventually leading to dysregulation of the neuroendocrine and immune systems and development of chronic conditions such as depression and metabolic syndrome (Lupien, McEwen, Gunnar, & Heim, 2009).

While the stress system evolved over millions of years as a necessary survival tool in response to ancient threats, modern society is vastly different from the environment experienced by our ancestors. We do not face threats of predation, and many once-deadly conditions are now easily remedied by modern medicine. Instead, humanity is exposed to psychosocial stressors on a day-to-day basis in the form of worry about a loved one, being bullied at school, seeing upsetting news on television, or upcoming deadlines with work, all of which can result in activation of the stress response. These situations were not encountered by our ancestors, but nevertheless our biology remained the same, crafted over eons by natural selection to respond adaptively to threatening stimuli. Hence, the commonplace 21st-century associations between stress, poor health, and accelerated aging.

Development of Aging Theory

Theories of aging have long addressed why and how we age (Kirkwood & Austad, 2000). Although cellular theories of aging were not established until the 19th century, ideas concerning the nature of bodily aging were conceived in ancient literature. Greek philosophers considered aging to be the process of the body becoming colder and drier, or an imbalance of bodily fluids (i.e., the four humors). These ideas dominated intellectual thinking for centuries, until the anatomical theory of disease emerged during the Enlightenment. This theory stipulates that the origins of disease lie in the body's internal organs and muscular and skeletal systems. This sparked increasingly rigorous investigation over the years into human biology as the source of aging and disease. Fueled by scientific milestones like Theodor Schwann's cellular theory (Schwann, 1839), describing cells as the most basic unit of life, cellular theories of aging began to emerge in the late 19th century.

Critical to this development was the work of the experimental biologist August Weismann. His hypotheses were situated in a life history approach to biology—namely, that there was a cellular mechanism to remove older, more fragile individuals from the population to liberate resources for those younger and healthier. He suggested that the lifespan was "bound to the number of somatic cell generations which follow after each other in the course of an individual life, and that this number, as well as the duration of individual generations of cells, is already determined in the germ cell" (Weismann, 1892, p. 50). This idea of limited cellular proliferation was not tested experimentally until the early 1960s, when Hayflick and Moorhead (1961) cataloged limited numbers of cell divisions, known as the *Hayflick Limit*, before cells entered a state of senescence, or replicative arrest. Senescent cells no longer divide, but remain metabolically active to produce signaling molecules that can damage the surrounding cells (Campisi, 2013). Importantly, the accumulation of senescent cells with age has been proposed as a driver of system decline (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013).

Despite this groundbreaking work, it was not known what mechanism within cells explained the limited cellular lifespan theorized by Weismann and observed by Hayflick. Further insight into this phenomenon was provided independently by Alexey Olovnikov and James Watson a decade later. Both described the end-replication problem with chromosomal DNA (Olovnikov, 1971; Watson, 1972). Specifically, at the end of each chromosome are *telomeres*, regions of repetitive DNA sequence that serve to protect and stabilize the chromosome. Each time the cell divides, between 12 and 30 base pairs of telomeric DNA are lost due to inefficiency in the DNA replication machinery's ability to copy it to the end (i.e., the 'end-replication problem'). This discovery lent support for the Hayflick Limit, suggesting that the limited number of cell divisions was related to the progressive shortening of telomeres (hence their regard as cellular aging "clocks").

Future research revealed that senescence was triggered when telomeres become critically short (di Fagagna, Reaper, Clay-Farrace, & Flegler, 2003) (Fig. 1).

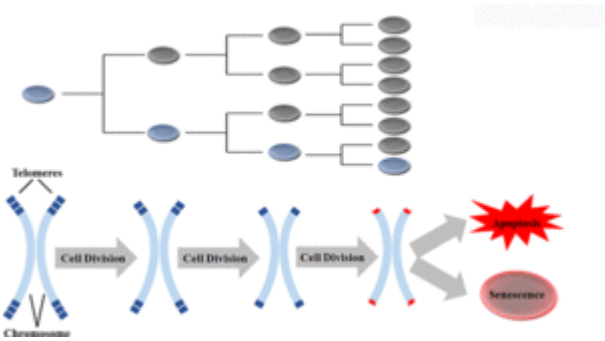

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Figure 1. Telomeres are protective nucleoprotein regions at the end of chromosomes that shorten each time that a cell divides. They are critical to cellular health and stability. Once they become critically short, cell death (apoptosis) and replicative arrest (senescence) pathways are activated.

Also important to consider with regard to cellular aging is Denham Harman's free radical theory of aging (Harman, 1956). He hypothesized that cells accumulated DNA damage from free radicals produced during normal cellular respiration, a process called *oxidative stress*. This damage continued to accumulate over time until the cell could no longer function properly, at which point programmed cell-death pathways are activated (i.e., apoptosis). Importantly, mitochondria are the primary source of free radicals in the cell. The so-called 'powerhouse of the cell,' mitochondria are responsible for generating the energy needed for cellular metabolic activity in the form of adenosine triphosphate (ATP). In addition to ATP, mitochondria produce harmful free radicals in 1%–3% of reaction catalyzed during cellular respiration (Valko et al., 2007). Mitochondria also contain their own DNA, independent of nuclear DNA but subject to the same damage from free radicals. In light of this, Harman updated his theory, citing mitochondria as governors of biological aging, wherein a feed-forward loop of mitochondrial DNA damage leads to increased free radical production and accelerated aging (Harman, 1972).

Over the next few decades, increased evidence would further link these two lines of inquiry. The discovery of the enzyme telomerase provided further insight into the cellular response to the end replication problem. Telomerase adds telomeric repeats to the end of chromosomes during cell division, thereby decelerating the rate of telomere erosion over time (Greider & Blackburn, 1985). While telomerase can protect the telomeres and extend the lifespan of certain cells (i.e., stem and germ cells), most somatic cells exhibit little to no telomerase activity, and as a result, their telomeres shorten with age (Harley, Futcher, & Greider, 1990). The causal link of mitochondria in this process was shown when oxidative stress accelerated the shortening of telomeres (von Zglinicki, Saretzki, Docke, & Lotze, 1995). Current theories, such as the mitochondrial-telomere axis of aging, unify early theories and situate telomeres as an aging phenotype, with mitochondria serving as a significant driving force (Sahin & DePinho, 2012). The next section expands on how stress interacts with these structures, leading to cellular aging.

Psychological Stress: A Driving Force in Cellular Aging

Stress is distinctly related to aging. As detailed in the "DEVELOPMENT OF AGING THEORY" section, *biological* stress (i.e., chronically elevated cortisol level concentrations, oxidative stress) can damage and age individual cells. This section expands on the various aspects of *psychological* stress and their impacts on cellular aging, with a focus on telomeres and mitochondria.

Psychological Stress and Telomeres

It is generally accepted that telomere length (TL) decreases with chronological age, due to the 'end replication problem.' However, the rate of shortening varies across the lifespan. It is suggested that the greatest loss occurs in the first years of life, corresponding with a rapid growth rate and high production and turnover of cells, followed by a stable plateau into childhood and young adulthood and a gradual decline into old age (Frenck, Blackburn, & Shannon, 1998). Beyond this natural erosion of telomeres by age, research has shown that the rate of telomere shortening is influenced by physical, psychological, and social conditions, resulting in their regard as a biological clock for studying accumulated cellular aging throughout the life course. Shorter telomeres are associated with increased incidence of age-related conditions like cardiovascular disease, diabetes, and stroke, independent of traditional risk factors (D'Mello et al., 2015; Haycock et al., 2014). Furthermore, in a large population study including 64,637 individuals, a significant association was observed between short TL and all-cause mortality (Rode, Nordestgaard, & Bojesen, 2015). By contrast, centenarians (those living longer than 100 years), are characterized by exceptionally long telomeres and increased cognitive function (Atzmon et al., 2010).

Stress can influence the rate of telomere erosion and consequently accelerate aging. In particular, stress during early life and the resulting developmental influences are known to have powerful effects on aging processes in later life (Heim & Nemeroff, 2001; Miller, Chen, & Parker, 2011). From the evolutionary perspective, this represents a developmental trade-off, prioritizing accelerated maturation to increase the probability of reproducing in a high-stress environment, at the cost of long-term health via accelerated aging (Belsky & Shalev, 2016). Telomere erosion has been suggested as a mediator of that process, linking early-life stressful experiences with accelerated aging. For example, in a prospective cohort study by Shalev and colleagues, common complications at birth, such as premature delivery or low birth weight, were linked with two aging indicators at age 38 years—short TL and older facial appearance—independent of family history, social risks, and life-course health (Shalev, Caspi, et al., 2014). The consequences of stress at birth, particularly psychological stress, are evident in two other studies. In the first small-

sample study, greater maternal stress during pregnancy was linked to shorter TL in offspring (Entringer et al., 2013), a finding that was replicated in another study using a prospective design over the whole course of gestation (Marchetto et al., 2016). The age-accelerating effects of early stressful conditions is further exemplified by research in individuals exposed to childhood adversity (e.g., institutionalization, sexual abuse, emotional abuse, neglect, etc.). Since Tyrka et al. (2010), dozens of studies have reported associations between childhood stress and shorter telomeres in adulthood (reviewed in Price, Kao, Burgers, Carpenter, & Tyrka, 2013; Shalev, 2012). These studies highlight the connection between childhood adversity and accelerated aging in later life. For example, greater exposure to institutional care (though of poor quality) was associated with shorter TL in middle childhood (Drury et al., 2012).

However, conclusions from these studies have been limited by their cross-sectional, retrospective design, which measures TL only after the exposure. That is, despite evidence of shorter telomeres in those that experienced adversity, it was unclear whether adversity actually *caused* shorter telomeres. In other words, survivors of early adversity may have presented with shorter telomeres before the adverse exposures, suggesting shorter telomeres may have bestowed a predisposition to adversity. Subsequent longitudinal research involving repeated measurements of TL within individuals provided critical prospective evidence. Specifically, children exposed to multiple types of violence between the ages of 5 and 10 years showed significantly more telomere erosion over time (i.e., by age 10) than did other children (Shalev, Moffitt, et al., 2013).

While stress in early life can predispose individuals to accelerated aging and shorter TL, chronic stress across the lifespan also plays a significant role. The foundational work in this area was by Epel et al. (2004), which showed a relationship among maternal caregiving (a chronic psychological stressor), shorter telomeres, and decreased telomerase activity. Follow-up studies provided further support of this point, showing that caregivers of Alzheimer's patients, as well as sisters of women with breast cancer, displayed similar associations with TL (Damjanovic et al., 2007; Parks et al., 2009). Likewise, chronic physical stressors, such as poor sleep quantity/quality, also have been linked with shortened telomeres (Liang et al., 2011).

When it comes to behavioral factors, these can either mitigate or exacerbate the effects of chronic stress on telomeres. For example, negative health behaviors like smoking and substance abuse are associated with shorter TL (Pavanello et al., 2011; Valdes et al., 2005). On the other hand, exercise has been shown to mitigate the effects of chronic stress on TL (Puterman et al., 2010), as well as mindfulness meditation, which has been shown to increase telomerase activity (Jacobs et al., 2011; Schutte & Malouff, 2014), suggesting a protective effect on the rate of telomere erosion. The association between mindfulness and telomerase activity was mediated by changes in feelings of perceived control and trait neuroticism, highlighting the relationship between psychological well-being and aging.

Conversely, mental health conditions, like depression, anxiety disorders, or posttraumatic stress disorder, represent states of chronic psychological duress. It is not surprising, then, that these same conditions also are associated with shorter TL (Jergovic et al., 2014; O'Donovan et al., 2011; Shalev, Moffitt, et al., 2014; Simon et al., 2006). Further, these internalizing disorders are highly comorbid with age-related physical illnesses like cardiovascular disease, diabetes, and cancer, which themselves have been linked with telomere shortening (Anderson, Freedland, Clouse, & Lustman, 2001; Mehnert & Koch, 2008; Roy-Byrne et al., 2008; Whooley et al., 2008).

Alongside evidence supporting the relationship among telomeres, stress, and aging are studies challenging the validity of TL measurements and their association with morbidity and mortality. Some reports show significantly weaker associations between TL and mortality in the exceptionally old (Martin-Ruiz et al., 2005), while others find alternative aging biomarkers (like inflammation) better capture the risk of morbidity and mortality (Glei, Goldman, Weinstein, & Risques, 2014). Such inconsistent findings may derive from variability in approaches to measure TL across studies. Despite relative agreement regarding the tissue source (i.e., blood), varied technologies to extract DNA (Cunningham et al., 2013) and subsequently quantify telomeric content (e.g., polymerase chain reaction and Southern blot) can affect the final measure reported and produce discrepancies in findings (Aubert, Hills, & Lansdorp, 2012).

Even so, the preponderance of epidemiological evidence, as well as a meta-analysis of over 20 studies investigating perceived stress and telomeres (Mathur et al., 2016), suggests that TL shortens in response to stress, and that telomere shortening predicts age-related disease and disability. Therefore, telomeres may serve as a cellular measuring stick, indicating the cumulative effect of psychological and physical stressors experienced across the lifespan. At the same time, they serve as a biological clock, counting the years that pass in their continual shortening. We now turn to mitochondria to describe more of the physiological changes associated with stress and cellular aging.

Psychological Stress and Mitochondrial Function

Although there are similarities between the cellular characterizations of mitochondria and telomeres, mitochondria are generally more complex. A single somatic human cell has 92 telomeres, representing the 23 chromosomes per human cell, or 46 chromatids with a telomere at each end. The TL varies across chromatid ends, including opposite ends of the same chromatid. In contrast, the mitochondrial copy number (the number of mitochondria within a cell) varies as a function of cell type. Red blood cells, for example, have no mitochondria, while liver cells can have more than 2,000 (Veltri, Espiritu, & Singh, 1990). Similarly, the sequence of mitochondrial DNA (mtDNA) varies among different mitochondria of a single cell, a property known as *mitochondrial heteroplasmy*.

The link between mitochondria and aging is also complex. Several features of mitochondria change across the lifespan. There is a marked decline in the respiratory activity of mitochondria within the aging tissues of the brain, skeletal muscle, and heart, which may underlie age-related cognitive decline, muscle weakness, and risk of heart disease, respectively (Cooper, Mann, & Schapira, 1992; Lesnefsky, Moghaddas, Tandler, Kerner, & Hoppel, 2001; Ojaimi, Masters, Opeskin, McKelvie, & Byrne, 1999). This decreased activity is associated with increased mutations, or changes to the native mtDNA sequence, which also accumulate over time (Wei, 1998). As such, mitochondrial heteroplasmy is positively associated with age (Sondheimer et al., 2011). At birth, there is a small amount of variation among an individual's mtDNA sequences. However, mitochondrial sequences become increasingly mutated across the lifespan, either through spontaneous mutations or an age-associated deletion of mtDNA (Corral-Debrinski et al., 1992; Michikawa, Mazzucchelli, Bresolin, Scarlato, & Attardi, 1999).

Abnormal mtDNA can be deleterious for several reasons. First, mtDNA deletions predispose cells to apoptosis, or programmed cell-death (Schoeler et al., 2005). Second, as more mitochondria are mutated, cellular respiration becomes less efficient, resulting in more free radicals and oxidative stress. Importantly, mtDNA is more susceptible to, and less likely to recover from, oxidative damage than nuclear DNA (Yakes & Van Houten, 1997). As a result, the relationship between mitochondria and stress is especially important as a driver of cellular aging.

As noted in the "WHAT IS STRESS?" section, stressful experiences translate to physiological changes that influence cellular processes, most notably cellular respiration and oxidative stress. As the site of cellular respiration, mitochondria stand at the gateway between psychological stress and cellular aging. Once released into the bloodstream, cortisol acts on target cells by permeating the cell membrane and binding to intracellular receptors within mitochondria (Manoli et al., 2007), thereby increasing ATP production and free radical generation, and as a result, oxidative stress. Scientists measure oxidative stress as the relative ratio between oxidants (the products of reactions between oxygen-containing molecules and free radicals produced by mitochondria) and antioxidants (the agents that reduce and eliminate oxidants). Oxidative stress can be measured systemically, such as the oxidative status of circulating plasma, or locally, such as the oxidative status of a specific tissue or cell type. Increased levels of oxidative stress are implicated in a spectrum of health conditions, including cancer, type II diabetes, heart disease, and neurodegenerative disorders (Droge, 2002). Further, the same chronically stressed maternal caregivers displaying shorter telomeres also exhibit greater levels of oxidative stress (Epel et al., 2004). Survivors of child maltreatment are similarly characterized by increased oxidative stress (Boeck et al., 2016). When it comes to mental health disorders, the evidence is more variable. While depression is characterized by increased oxidant status, anxiety-induced oxidative stress is marked by increased oxidants *and* diminished antioxidant defenses (Ng, Berk, Dean, & Bush, 2008).

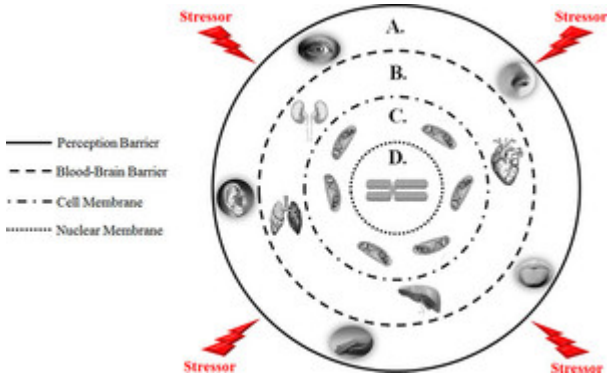

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Figure 2. **A. Person Level:** Environmental cues are detected by various sensory organs (vision, smell, hearing, touch, and taste). Sensory information is integrated into the brain. **A→B:** Stress-induced changes are transmitted to the periphery along the SAM and HPA axes of the central nervous system. **B. System Level:** Systemic effects, including increased respiration in the lungs, accelerated heart rate, glucose release from the liver, and secretion of cortisol from the adrenal glands atop the kidneys, promote survival during stress. **B→C:** Cortisol permeates the cell membrane to promote adaptation within cells. **C. Cellular Level:** Cortisol binds to receptors within mitochondria, stimulating cellular respiration and energy production in the form of ATP. **C→D:** Free radicals generated by mitochondria bypass the nuclear membrane to damage DNA oxidatively. **D. DNA Level:** DNA damage activates cell death pathways, leading to telomere shortening, cellular senescence, and accelerated cellular aging.

Mitochondrial changes occurring during stress represent physiological adaptation at the cellular level. Specifically, mitochondria divide during times of oxidative stress, increasing their copy number to meet an increased energetic demand (Lee, Yin, Lu, Chi, & Wei, 2000). However, mitochondrial replication machinery, as compared to the nuclear equivalent, is less able to detect and correct sequence errors that spontaneously occur during the division process. Therefore, increasing copy number increases the odds of acquiring a mutation in mtDNA, which may be preferentially passed to subsequent cellular generations (Diaz et al., 2002). Exposure to stressful life experiences is associated with alterations to copy number and heteroplasmy in the mitochondria of white blood cells. One study found that individuals with a history of childhood adversity, as well as those with chronic depression or anxiety, had higher copy numbers, as well as shorter telomeres (Tyrka et al., 2016). The intimate connection between mitochondria and telomeres is mediated by oxidative stress. Lifestyle behaviors like smoking, which shorten telomeres, are associated with increased oxidative stress, while those that protect telomeres, like exercise, are associated with decreased oxidative stress (Moller, Wallin, & Knudsen, 1996).

Taken together, the relationship between telomeres and mitochondria can explain how these two structures are influenced by stress to promote accelerated aging (Fig. 2). Mitochondria activate during times of stress, producing the energy necessary for immediate survival, but also increasing oxidative stress within cells. This adaptive response occurs at the cost of telomeres, which are prone to oxidative damage. In fact, studies with human cells indicate that telomerase colocalizes with mitochondria during times of oxidative stress, protecting the organelles responsible for energy production at the cost of telomeric stability (Ahmed et al., 2008). However, mtDNA is also susceptible to

oxidative damage that, when it occurs, is less easily repaired and more likely to persist to future generations of cells (Yakes & Van Houten, 1997; Diaz et al., 2002). As a result, passage of time, repeated exposure to stress, chronic psychological stress, and mental and physical health conditions can all result in mitochondrial dysregulation, elevated oxidative stress, and reduced TL, promoting cellular aging and impairing long-term survival.

Conclusions

Aging is a complex process mediated by physiological and cellular changes throughout the lifespan. While the structures highlighted herein, telomeres and mitochondria, represent those most directly implicated in cellular aging by decades of research, they are not exhaustive. For example, distinct epigenetic changes throughout the genome are also associated with aging (Koch & Wagner, 2011). Yet, the downstream effects of these epigenetic changes are still uncertain, and other evidence has implicated mitochondria as regulators of certain epigenetic processes (Shaughnessy et al., 2014). Systemic inflammation is also suggested to play a key role in the aging process (López-Otín et al., 2013). Notably, early-life adversity is associated with elevated inflammation (Danese et al., 2007). Furthermore, senescent cells with critically short telomeres release high levels of inflammatory factors (Merino et al., 2011), as do oxidatively damaged mitochondria (Green, Galluzzi, & Kroemer, 2011). Thus, systemic inflammation may derive from, rather than result in, telomere erosion and mitochondrial dysregulation.

Other composite algorithms determine biological age by including measures across several organ systems, genetic measures, and circulating biomarkers (Belsky et al., 2015). However, these models are relatively new and have not yet been operationalized in relation to psychological stress. A more novel area of interest is altered proteomics (the structure and dynamics of cellular proteins) across the lifespan. The mechanisms regulating protein homeostasis are still not well understood and continue to be an area of focus for future research. Nonetheless, several proteins already identified as key to the aging process are those related to mitochondrial function and telomere maintenance, further highlighting the importance of these two cellular structures. In summary, although short-term stress is an adaptive response allowing organisms to mobilize resources for survival, long-term stress, whether psychological, biological, or environmental, disrupts homeostasis to accelerate cellular aging by shortening telomeres and disrupting mitochondrial activity. A better understanding of the underlying mechanisms can help to promote therapeutic interventions to reduce (or even reverse) the damaging effects of stress on aging processes.

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