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Effect of DNA damage mediating psychosocial stress on aging

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Abstract

Adversity and psychosocial stress are involved in aging through the following pathways. psychological stress enhances the nerve system to secrete endocrine mediators (hormones). Mitochondrial respiration mediates energy production stimulated by binding to these hormones to their receptors. Energy produced by mitochondria accelerates metabolism and, in its turn, leads to increases in reactive oxygen species (ROS) of free radicals. Cellular stress and accumulation of damage can result from an excess of ROS. Accumulation of damage comprises damages in telomeric and nontelomeric DNA, in addition to mitochondrial DNA. Mitochondrial DNA damage plays an important role in increasing the pathway of p53/p21. The expression of the PGC-1α gene is inhibited by activation of the previous pathway that generates a decrease in mitochondrial biogenesis. The low level of mitochondrial biogenesis generates mitophagy defects and increases the level of dysfunctional mitochondria that lead to a high level of ROS production. Nuclear DNA damage and mitochondrial dysfunction stimulate necrosis or cell senescence. Necrotic cells enhance the inflammatory activity by which damage-associated molecular patterns (DAMPs) are continuously secreted. Senescent cells secrete high levels of the senescence-associated secretory phenotype (SASP) that includes tumor necrosis factor TNF-α and interleukin-6 (IL-6) as inflammatory cytokines, and MCP-2 and interleukin-8 (IL-8) as chemokines. All these processes work together to accelerate the biological aging process by causing defects related to aging such as diabetes and cardiovascular disease.

KeyWords: *DNA damage, psychosocial stress, aging*

Introduction

Psychosocial stress (Including work-related stress, low socioeconomic status, stressful life events, caregiving, loneliness, and low social support) may stimulate neurobiological stress that play an important role in causing disease aging, such as cardiovascular disease, therefore, this stress is accelerating the biological aging process. This stress correlates with the aging process when individuals are unable to recover from a stressor (1-3). Neurobiological stress activation can cause the sympathetic nervous system (SNS) to secrete norepinephrine (NE) and epinephrine (E) into blood vessels, and the hypothalamic-pituitary-adrenal (HPA) axis to secrete glucocorticoids (GC) into blood vessels, and HPA is a complex set of direct influences and feedback interactions among three components: the hypothalamus (a part of the brain located below the thalamus), the pituitary gland (a pea-shaped structure located below the hypothalamus), and the adrenal. Many physiological processes can be altered by the action of neuroendocrine mediators (including norepinephrine (NE), epinephrine (E), and glucocorticoids (GC)) that play a significant role in causing the biological aging process. Altering physiological processes can cause primary cellular changes represented by loss of proteostasis, epigenetic alterations, shortening of the telomere and DNA damage, and secondary cellular changes that refer to deregulated nutrient sensing, poor energy production from mitochondrial dysfunction and cellular senescence (Table 1). These primary and secondary cellular changes enhance the secretion of inflammatory factors and free radicals from senescent cells that represented by SASP and DAMPs and ultimately caused aging-related phenotypes by restricting the function of senescent cells. Disruption of higher-level functions in senescent cells can be described as biological aging (4-8). This review aimed to provide a detailed explanation of the primary and secondary

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cellular changes caused by altering physiological processes due to the action of neuroendocrine mediators resulting from the effect of psychosocial stress, ultimately causing the biological aging process.

Table 1 *Primary and secondary cellular changes of aging*

	Cellular changes of aging	Process
Primary Change	Instability of DNA	Occurrence of DNA damage that is represented by translocations, point mutations, and gain or loss in chromosome
	Telomeres shorten	Occurring of DNA damage in the telomere
	Alterations caused by Epigenetic	Occurrence of histone acetylation or methylation
Secondary Change	Proteostasis defect	Inability to remove unfolded proteins
	Mitochondrial Dysfunction	reactive oxygen species increase and decrease in ATP that is produced by mitochondria
	Cellular senescence	Secretion of DAMPs and SASP

DNA damage mediating the aging process.

Psychosocial stress stimulates the production of NE and E that binds β2-adrenoreceptors and leads to an increase in the level of enzyme protein kinase A (PKA); this enzyme increases the oxidative phosphorylation process and creates more ROS such as peroxide hydrogen, superoxide, and a singlet oxygen molecule. ROS attack DNA in the nontelomere region and mitochondrial DNA causing damage that stimulates the DNA damage response (DDR) pathway leading to necrosis or cellular senescence. Furthermore, the damaged region of the telomere in DNA due to ROS agents stimulates cellular senescence when the length of telomeres becomes short (9, 10). A study in humans showed that psychosocial stress increases DNA and RNA damage (11, 12). The experiment was carried out on rodents subjected to psychosocial stress such as social isolation, which showed that there is a significant increase in DNA damage compared to the control group (13, 14). Another study in humans revealed that exposure to psychosocial stress (Including work-related stress, low socioeconomic status, stressful life events, caregiving, loneliness, and low social support) generates stressed hormones such as NE and E that lead to increased DNA damage in various kinds of cells (15, 16). Cells exposed to oxidizing agents such as ROS and undergoing DNA damage activate the DNA damage response (DDR). The DNA damage response regulates three different processes such as DNA repair, apoptosis, and senescence. The cell containing damaged DNA will be arrested in the cell cycle until the damaged DNA is repaired or if repairing damaged DNA is impossible, the cell undergoes apoptosis or senescence (Figure-1) (17-19).

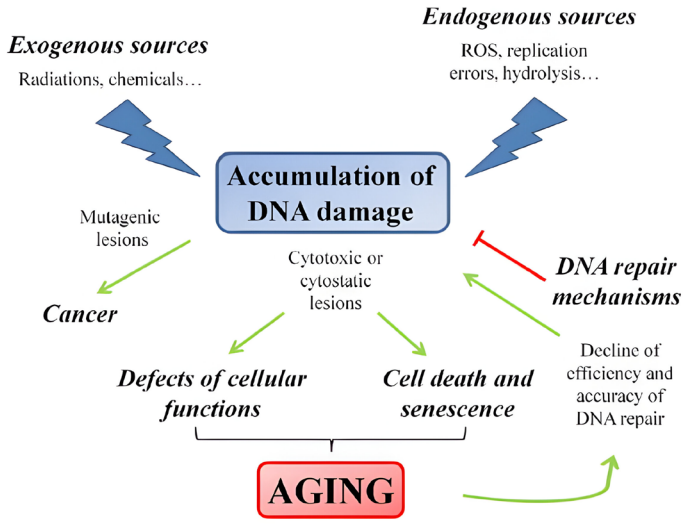

Figure 1: *Representation of the pathways that modulate the aging process.*

Telomere shortening mediating the aging process.

Telomere participate in stopping the aging. It is found at the end of the chromosome, and it naturally shortens at cell replication. However, the telomerase enzyme elongates the telomere and prevents it from shortening. The shortening of the telomere region due to exposure to high oxidant compounds triggers cellular senescence (20-22). The important maker of aging is telomere shortening, and many studies showed that there was a high telomere shortening in peripheral blood leukocytes for people who suffer from psychosocial stress, such as low social support and early life adversity (23, 24). Telomere shortening is also detected in newborns whose mothers are exposed to psychosocial stress (25, 26). Many studies showed that there is a correlation between telomere shortening and stress hormones such as E, NE, and GC. Increasing the stress hormones in the peripheral blood mononuclear cells (PBMCs) due to exposure to psychosocial stress is correlated with telomere shortening hence the process of biological aging is engaged (27-30). Telomere shortening is a natural process occurring at the end of the chromosome; however, DNA damage in the telomere may result in arresting of the cell cycle and senescence. However, exposure to mild oxidative stress leads to single-stranded breaks in the telomere and accelerates premature cell cycle arrest and senescence. Furthermore, exposure to acute stresses leads to double-strand breaks in the telomere and resulting in persistent DDR signaling (31-33) (Figure 2).

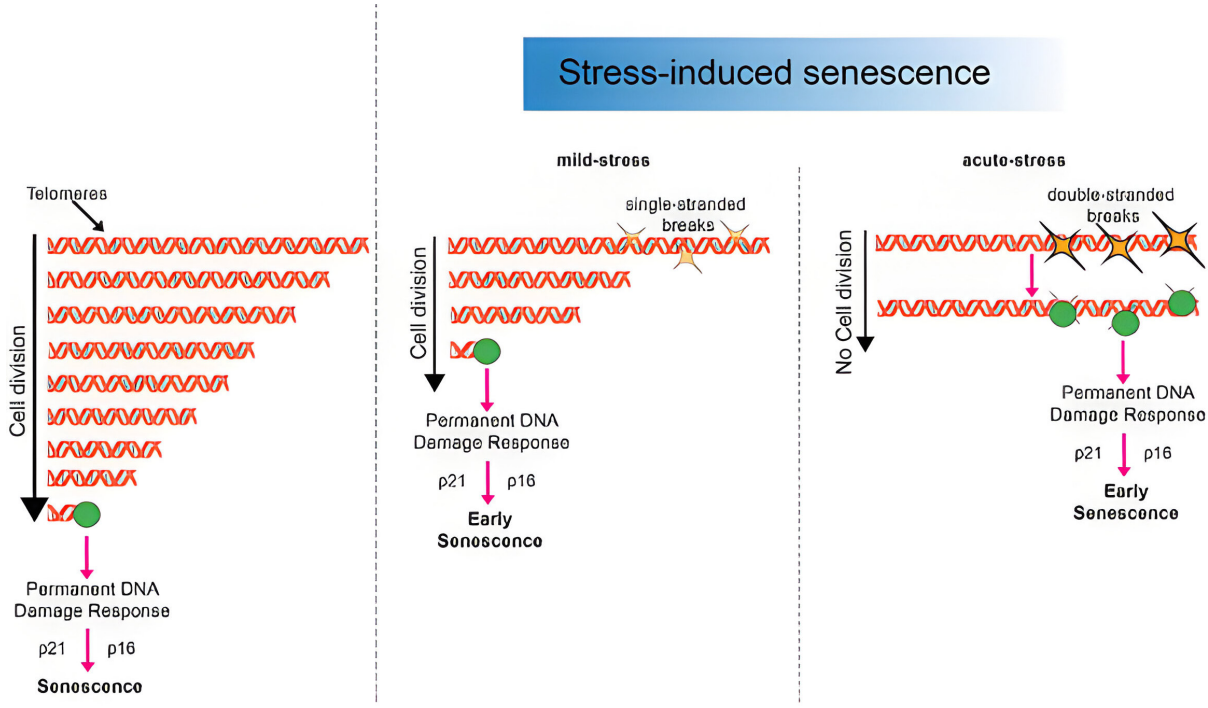

Figure 2: *Stress-induced telomere shortening and senescence.*

Mitochondrial dysfunction mediating the aging process.

As mentioned previously, one of the secondary cellular changes is mitochondrial dysfunction, which results from altering physiological processes due to the action of neuroendocrine mediators through exposure to psychosocial stress. Mitochondrial dysfunction can increase oxidative damage and decrease mitophagy (the process of removing dead or dysfunctional mitochondria). Increasing oxidative damage in dysfunctional mitochondria leads to telomere shortening that contributes to cellular senescence. A decrease in mitophagy in dysfunctional mitochondria leads to a decrease in the process of clearing dead or dysfunctional mitochondria. Dead or dysfunctional mitochondria produce a large amount of ROS that leads to shortening of the telomeres that contributes to cellular senescence (34, 35). The contribution of mitochondrial dysfunction to the aging process comes from the fact that the decline in mitochondrial function and health associated with mitochondrial dysfunction can affect the cell, organs and body. Mitochondrial dysfunction leads to age-associated cell decline (AACD) in the cell, then affects the organ by weakening the organ, such as muscles, and finally affects the body through a decrease in function and health problems such as reduced strength and mobility (36, 37) (Figure 3).

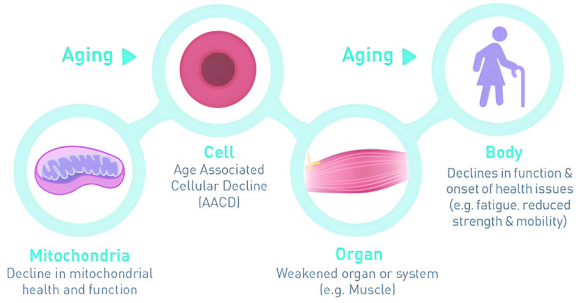

Figure 3: *Representation of the mitochondrial origin of age-related decline.*

Cellular senescence mediates the aging process

Arresting cell growth and proliferation without affecting metabolic processes refers to cellular senescence that drives age-related diseases. Factors that participate in cellular senescence are mitochondrial dysfunction, telomere shortening, and DNA damage that in turn leads to an increase in the level of the p53/p21 pathway (The p53-p21cip1 pathway appears to be more responsive than the p16-Rb pathway for the induction of endothelial cell senescence. This is because the knockdown of p53 expression, but not p16, inhibits endothelial cell senescence). Telomere shortening mediating cellular senescence is defined as replicative senescence, while DNA damage mediating cellular senescence leads to activation of the p53/p21 (38). Characteristics of cell senescence include alteration of signaling pathways that include DNA damage response (DDR), SASP, cyclin-dependent kinase (CDK), and morphological changes. DDR is responsible for recognizing DNA damage and establishing repair, while CDKs are a group of proteins that function as a regulation of cell cycle progression such as p16INK4a and p21 that are involved in senescence. SASP consists of a group of inflammatory cytokines, chemokines, and DAMPs that drive age-related diseases and hence cellular senescence. Regarding morphological changes, the senescence cell has an irregular shape and increased lysosomal content (39-41). A study carried out in mice revealed that mice exposed to stress can activate pathway of p53/p21 and p16INK4a and p21 that are involved in senescence (42, 43). Another study showed that injection of mice with endocrine mediators can activate pathway of p53/p21that is involved in senescence (44). Exposure to stress leads to the induction of cellular senescence that produces SASP. SASP helps in senescent cell accumulation, and impairs clearance and production of chronic inflammation (45) (Figure-4).

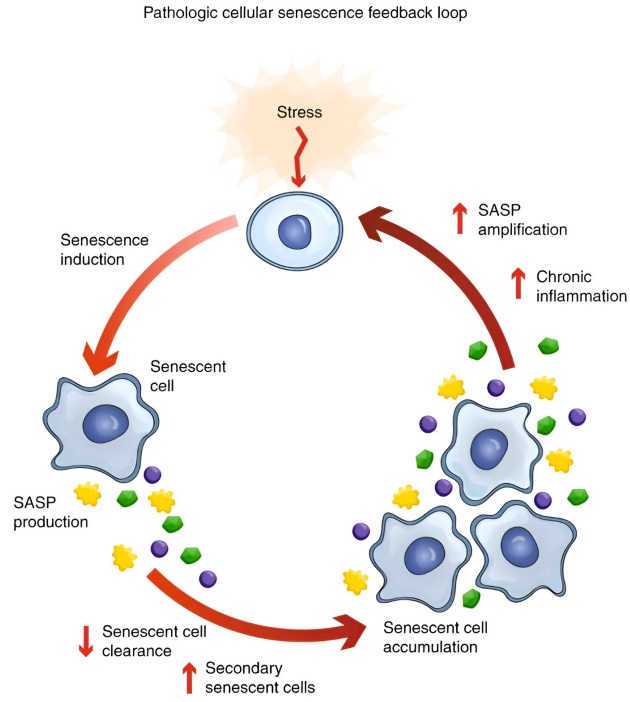

Figure 4: *Representation of the accumulation of senescent cells by SASP.*

Inflammation mediating the aging process

Inflammation triggered by psychosocial stress and neuroendocrine mediators leads to damage and destroys the cell and nearby tissue that drive the biological aging process. Nuclear factor (NF-κB) transcription factors are stimulated by binding NE to beta-adrenergic receptors, and this leads to the production of tumor necrosis factor (TNF). Conversely, NF-κB transcription factors are inhibited by binding to GC with their receptors, leading to a decrease in TNF production. Many studies carried out in human and mouse models showed that psychosocial stress leads to the production of TNF. Furthermore, psychosocial stress decreases glucocorticoid receptors that lead to a low level of binding of GC to receptors and again activation of Necrosis Factor (TNF)-α, these pro-inflammatory cytokines stimulate the biological aging process (46, 47). Other studies showed that binding of NE to beta-adrenergic receptors leads to increases in CD8 T, IL-6 and IL-10 that participate in the onset of aging-related disease (48, 49). The inflammation of aging is derived from different sources, mainly mitochondrial dysfunction and increased senescent cells (50) (Figure-5).

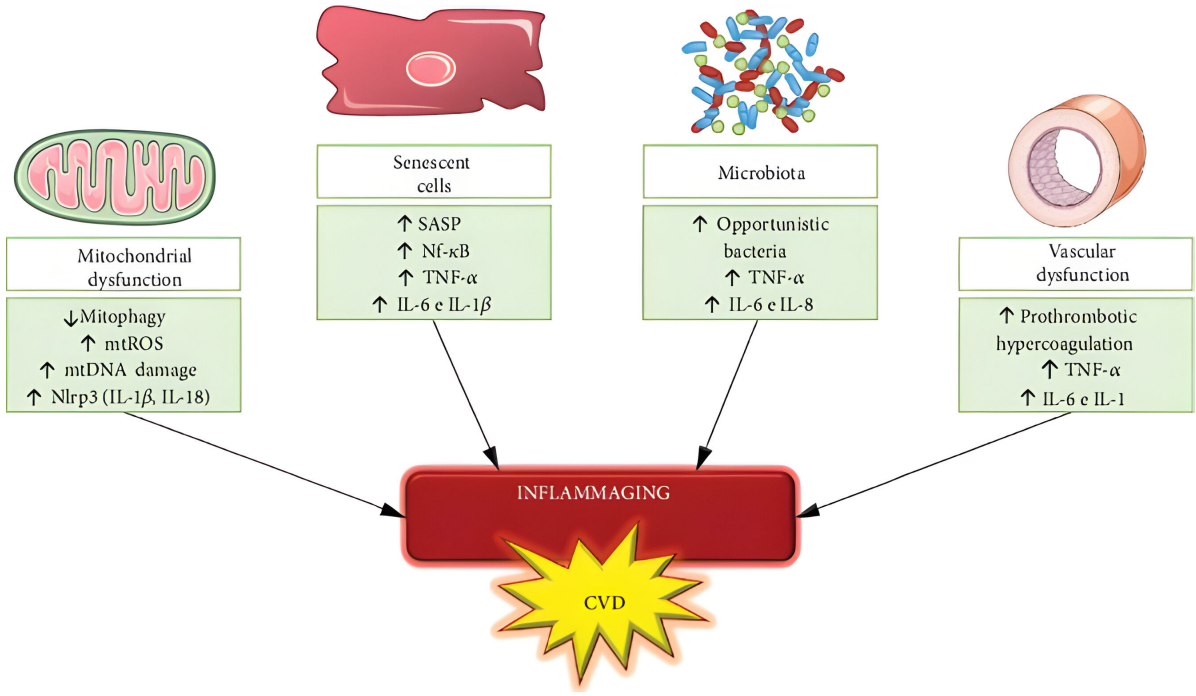

Figure 5: *Schematic representation of the inflammaging source. TNF (Tumor necrosis factor), IL (interleukin), NF (necrosis factor) and SASP (senescence-associated secretory phenotype).*

Conclusions

In summary, psychosocial stress and associated neurobiological response participate in the biological aging process by increasing the risk of age-related disease. The biological pathways involved in accelerating aging are DNA damage, shortening of the telomere length, mitochondrial dysfunction, cell senescence, and the inflammatory response.

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