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Oxidative Stress, Aging, and Short Peptides

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This article reviews oxidative stress as one of the mechanisms impairing the functions of cells, organs, and tissues. Aging is associated with reductions in the activities of the enzymes of the antioxidant system. Reactive oxygen species formed in oxidant stress damage DNA, RNA, proteins, and lipids, leading to cell apoptosis. Neurodegenerative changes can develop in conditions of oxidant stress and mitochondrial dysfunction. A potential direction in the treatment of neurodegenerative pathology consists of using antioxidants such as melatonin or the short peptides AEDG and KE. Peptide AEDG stimulates endogenous melatonin synthesis as the body ages, while peptides AEDG and KE have antioxidant and geroprotective properties, normalizing telomere length and preventing cell apoptosis. Studies of oxidative stress at the cell, organ, and tissue levels are important for gerontology and the search for novel approaches to the treatment of neurodegenerative diseases.

Keywords: oxidative stress, aging, neurodegenerative diseases, short peptides.

Abbreviations: ATP – adenosine triphosphate; RNS – reactive nitrogen species; ROS – reactive oxygen species; AD – Alzheimer's disease; PD – Parkinson's disease; DNA – deoxyribonucleic acid; OS – oxidative stress; AEDG peptide – Ala-Glu-Asp-Gly; KE peptide – Lys-Glu; RNA – ribonucleic acid; PHA – phytohemagglutinin; HTT – huntingtin protein; KEAP – Kelch-like ECH protein; NAD – nicotinamide adenine dinucleotide; NMDAR – N-methyl-D-aspartate receptor; PK – protein kinase; PTEN – phosphatase and nestin homolog; SOD – superoxide dismutase; TRF – telomere repeat factor.

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The free-radical theory of aging suggests that the protective mechanisms of the body are unable to respond to damage produced by reactive oxygen species (ROS) [44]. Oxidative stress (OS) is imbalance between prooxidants and antioxidants and leads to impairments to oxidative-reductive signaling and damage to functionally active molecules in cells [12, 45]. OS increases with age and affects the normal functioning of tissues and organs. OS participates in the pathogenesis of age-associated diseases: neuropathology, diabetes mellitus, atherosclerosis, cardiovascular pathology, renal failure, and respiratory failure, skeletal muscle dysfunction, various forms of arthritis, dementia, obesity, osteoporosis, metabolic syndrome, and malignant neoplasms [32].

Cells generate ROS as a side product of chemical reactions in the process of cellular respiration or in response to stressors [23]. ROS include the superoxide anion radical, nitric oxide, hydrogen peroxide, the hydroxyl radical, peroxynitrite, and other compounds [30]. ROS are produced in mitochondria and peroxisomes by mechanisms involving the NADPH oxidase family, monoamine oxidase, and other enzymes.

The antioxidant system includes low molecular weight substances competing with ROS for cell structures: vitamins, glutathione, lipophilic antioxidants, and uric acid.

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Antioxidants in most cases neutralize ROS as a result of direct chemical reactions leading to the formation of large quantities of less reactive or inert products. Superoxide dismutase (SOD) is expressed in response to the appearance of ROS and converts oxygen superoxide into hydrogen peroxide. Hydrogen peroxide is converted by catalase or glutathione peroxidase into water and oxygen. Glutathione disulfide produced by glutathione peroxidase during the reduction of peroxides is then again reduced by glutathione reductase [43]. Other antioxidant proteins are able to bind redox-active transition metals, maintaining them in the inactive form. Iron and copper can interact with hydrogen peroxide to form the highly active hydroxyl radical [51].

Another mechanism of protection from OS consists of activation of nuclear factor Nrf2. Nrf2 binds Kelch-like ECH protein 1 (KEAP1), which acts as a substrate adapter supporting ubiquitinylation and Nrf2 degradation by ubiquitin ligase E3 Cullin-3 [25]. In the presence of oxidizers, KEAP1 releases Nrf2 with subsequent translocation to the nucleus, where it activates the transcription of cytoprotector genes via promoter sequences containing conserved elements of the antioxidant response [17]. This increases the level of antioxidant enzymes and proteins such as glutathione-S-transferase, NAD, quinoxidoreductase-1, SOD, glutathione peroxidase, hemoxygenase-1, glutamate cysteine ligase, thioredoxin, and catalase, and also promotes mitochondrial biogenesis, supporting replacement of damaged organelles [37]. Some enzymes are able to restore ROS-damaged proteins, though this is often impossible. In most cases, oxidation-damaged proteins are removed by proteolysis mediated either by the ubiquitin-proteasome system or the lysosome system.

Oxidative stress, aging, and age-related diseases. The synthesis of ROS and reactive nitrogen species (RNS) is part of the normal aerobic cellular metabolism. Active synthesis of ROS and RNS occurs in stress and on development of age-related diseases. At the same time, ROS, which are side products of chemical reactions in the body, when present at low concentrations can carry out regulatory functions [8, 20]. In OS, the intensity of ROS and RNS synthesis are greater than the antioxidant activity of the defensive systems of the cell. Damaged molecules neither corrected by the cellular repair system nor degraded lead to apoptosis or replicative cell aging. These are the processes underlying aging [53].

The brain is sensitive to oxidative imbalance because of its high energy requirement, increased energy consumption, and large quantities of easily oxidized polyunsaturated fatty acids [52]. As compared with other organs, the brain contains significantly smaller quantities of antioxidants. This hinders ROS neutralization, such that ROS accumulate in the hippocampus, striatum, and hypothalamus on aging, which promotes neuron apoptosis and cognitive decline [35].

The endothelium of brain vessels is also a target of OS. Accumulation of ROS in vessel walls induces endothelial dysfunction and is involved in the pathogenesis of cerebrovascular diseases. The vascular network of the brain becomes more vulnerable to inflammatory processes, facilitating increases in free radical formation [40].

ROS production in skin fibroblasts has been shown to be generated by modulation of phosphatidylinositol-3,4,5-triphosphate metabolism. Increased ROS production in replicative aging of fibroblasts can be blocked by inhibition of three signal pathways: PI3K, protein kinase C, and NADPH oxidase. Decreases in PTEN (phosphatase and tensin homolog) levels promote reductions in the quantity of ROS in human skin fibroblasts [36].

Nucleotides are among the main targets of OS. ROS can produce breaks in DNA chains and modifications to bases, leading to changes in gene activity and impairment of cellular metabolism. OS promotes reductions in telomere length, replicative cell aging, and decreased longevity. This is associated with reductions in telomerase activity – this being an enzyme which not only regulates telomere length but also protects mitochondria from OS [16].

Telomere length is influenced by the following factors: genetic predisposition, sex (females have longer telomeres than males, perhaps due to the antioxidant activity of estrogens), ethnic group (Europeans have longer telomeres than members of negroid races), stress (stress and depression increase oxidative stress levels, which in turn decrease telomere length and telomerase activity), physical activity (moderate physical activity increases telomere length), obesity (associated with chronic inflammation and increased ROS, leading to decreased telomere length), and smoking and alcohol (which decrease telomere length) [49]. 8-Oxoguanine induced by oxidative stress changes the ability of TRF1 (telomere repeat factor 1 – a homodimer binding double-stranded TTAGGG telomere sites and having the ability to inhibit telomere lengthening by telomerase) and TRF2 (telomere repeat factor 2 – a homodimer binding with the same site as TRF1 but preventing recognition of double-stranded DNA breaks as damage needing repair) to bind telomere sequences. Decreases in TRF1 and TRF2 binding are responsible for arrest of replication forks and shortening or dysfunction of telomeres, which in turn induce aging and chromosome instability (Fig. 1) [16].

During oxidative stress, SRC kinase phosphorylates the catalytic subunit of TERT telomerase. This is followed by export of TERT from the nucleus using CRM1 protein. TERT is transported into mitochondria by TIM and TOM proteins. In mitochondria, TERT binds with a set of genes in mitochondrial DNA, inducing mitochondrial oxygen consumption (Fig. 2) [42].

However, many protein and lipid oxidation products can be useful for cell survival. These compounds are usually formed at OS of moderate intensity. This type of stress is part of the adaptive response (Fig. 3) [13].

Oxidative stress and neurodegenerative diseases. The functions of the hippocampus can be impaired by de-

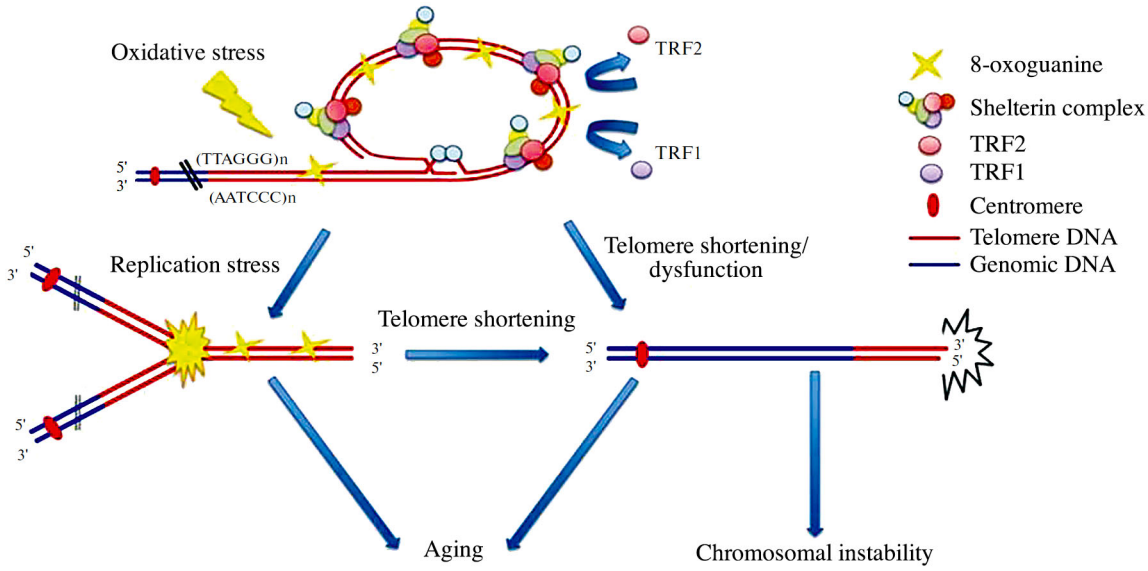

Fig. 1. Oxidative stress, telomere dysfunction, and aging (from [16] with modifications).

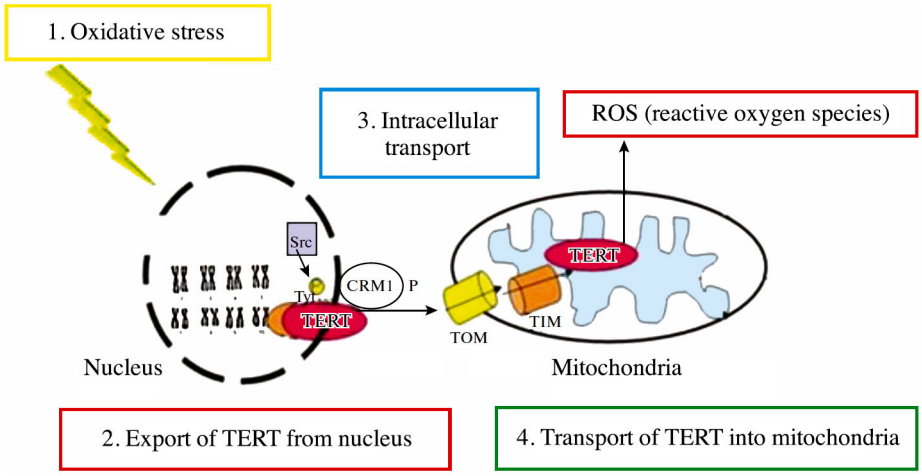

Fig. 2. Oxidative stress, telomere and cell aging (from [42] with modifications).

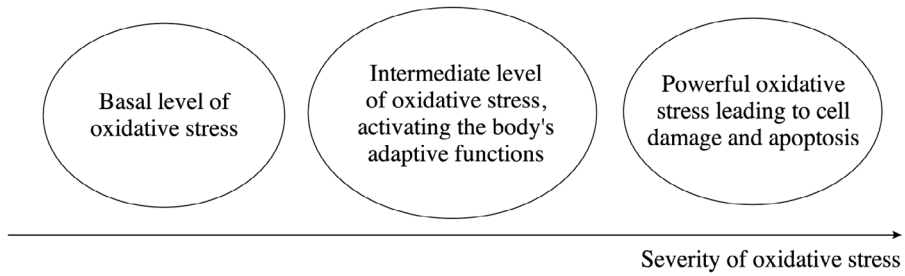

Fig. 3. Levels of oxidative stress and its influence on cellular homeostasis (from [53] with modifications).

creasing the antioxidant activity of enzymes and irradiating with low-dose radiation, which are accompanied by deficit of extracellular SOD [24]. Learning and memory functions decline, neurogenesis decreases, and the number of spines on hippocampal neuron dendrites drops [54]. Aging is also associated with an increase in the production of prooxidants and the accumulation of oxidation end products. Impairments to hippocampal functions in SOD deficiency, on exposure to ionizing radiation, and in natural aging have common mechanisms. Tissue levels of protein, lipid, DNA, and RNA oxi-

dation increase with age, explained by the increase in ROS production and the decrease in the activity of the antioxidant system [40, 41].

OS plays a significant role in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's chorea (HC), lateral amyotrophic sclerosis, and Friedrich's ataxia. Mitochondrial dysfunction develops in all these states and is accompanied by impairment to energy metabolism and the subsequent death of nerve cells [23, 47].

Increased ROS production associated with mitochondrial dysfunction and decreases in the antioxidant activity of the body's defense system decreases synaptic activity, leading to cognitive dysfunction. OS and mitochondrial dysfunction form a pathophysiological arc, which plays an important role in the pathogenesis of AD. Furthermore, ROS damage nuclear and mitochondrial DNA, lipids, and proteins regulating calcium homeostasis and other neuron functions. Anomalous cellular metabolism can in turn affect the production and accumulation of toxic β-amyloid and hyperphosphorylation of τ protein [47].

OS and free radical formation, along with excitotoxicity, lead to apoptosis of hippocampal neuron [38]. At the same time, excitotoxicity and free radical formation, along with activation of N-methyl-D-aspartate receptors (NMDAR) and impairments to synaptic functions induced by OS, are directly related to the pathogenesis of AD. Furthermore, the mechanism of action of oxidative-reductive stress on synapses is associated with changes in the expression of NMDAR. It has been suggested that OS mediated by NMDA receptors and their interactions with other molecules may be the moving force leading to hyperphosphorylation of τ protein and synapse dysfunction [27]. The increases in the cytoplasmic calcium concentration seen in AD trigger intracellular cascades, leading to increased ROS levels, increases in OS, and degradation of cognitive functions [19]. The accumulation of toxic β-amyloid peptide in hippocampal neurons activates stress-linked kinases PKC, PKA, and CaMKII, facilitating the development of OS and apoptosis. Understanding of the role of OS in metabolic impairments in hippocampal neurons may be of decisive significance for the development of therapeutic strategies directed at preventing the development of AD [26]. Astrocytes play an important role in the pathogenesis of degenerative diseases. Impairments to astrocyte functions lead to the development of OS, inflammatory reactions, and glutamate toxicity [35].

Telomere shortening, OS, DNA damage, the age-associated secretory phenotype of cells, and mitochondrial dysfunction promote faster neuron aging [18]. Other studies have identified an interaction between decreased telomere length in blood leukocytes and increases in the risk of developing AD [21, 34].

OS has been suggested to be an etiopathogenetic factor not only in AD, but also in other degenerative disorders, because of impairments to the regulation of antioxidant responses leading to mitochondrial dysfunction [23].

The main pathological features of PD are loss of dopaminergic neurons and accumulation of Lewy bodies containing α-synuclein. In PD, the activity of mitochondrial complexes I and IV in dopaminergic neurons of the substantia nigra is inhibited [50]. α-Synuclein can be imported into mitochondria and bind with the inner mitochondrial membrane in dopaminergic neurons. Overexpression of α-synuclein exacerbates mitochondrial dysfunction, OS, and neuropathology induced by inhibition of complex I, while deficit of α-synuclein weakens these effects [39]. At the same time, monomeric α-synuclein can interact with ATP synthase, leading to increased ATP production. Furthermore, aggregated α-synuclein induces changes in mitochondrial membrane permeability, leading to swelling and cell apoptosis [33].

In HC, there is a manifold increase in the number of CAG triplets in the gene for huntingtin (HTT) protein, leading to polyglutamine repeats in the protein and decreases in the activity of mitochondrial respiratory complexes II and III [10]. At the same time, OS and inflammation are additional common pathogenetic factors for HC [11]. In an animal model of HC using inhibition of mitochondrial complex II, overexpression of the NFE2L2 gene had a neuroprotective effect. Cotransfection with NFE2L2 and mutant HTT in primary striatal neurons decreased the time taken for metabolism of the mutant HTT and improved cell viability [48]. Oxidative stress in AD and other neurodegenerative diseases is an unavoidable part of the pathological process, such that antioxidants may be useful in the treatment and prevention of these diseases [15, 23, 46]. However, positive results with antioxidants in neurodegenerative diseases can only be attained if the therapeutic agent is able to cross the blood:brain barrier and enhance the mechanisms of endogenous antioxidant defense [14]. Furthermore, compounds able to modulate ROS production, such as melatonin [22] or endogenous pineal peptides stimulating its production [3, 5], may be of value in the treatment and prevention of AD.

Peptides AEDG and KE, geroprotection, and oxidative stress. The short peptides AEDG and KE, which have antioxidant properties, promote increases in telomere length by activating telomerase. Peptide AEDG (Ala-Glu-Asp-Gly, Epitalon) is a regulator of the functions of the pineal, the retina, and the neuroimmunoendocrine system; it is found in the polypeptide complex of the pineal [5]. Peptide AEDG normalizes the nocturnal secretion peak of the hormones melatonin and cortisol in elderly animals and people, has immunoprotective and oncostatic actions, and increases mean and maximum durations of life of experimental animals [1, 9]. Addition of peptide AEDG to human embryo fibroblast cultures induces the expression of the telomerase gene and activates the telomerase enzyme itself, leading to increases in telomere length by a factor of 2.4 [28, 29].

Peptide KE (Lys-Glu, Vilon) is a member of the thymomimetic peptides group, is found in the polypeptide complex, and is used in the medicine Thymalin. Peptide KE stimulates innate and adaptive immunity and has activatory effects on

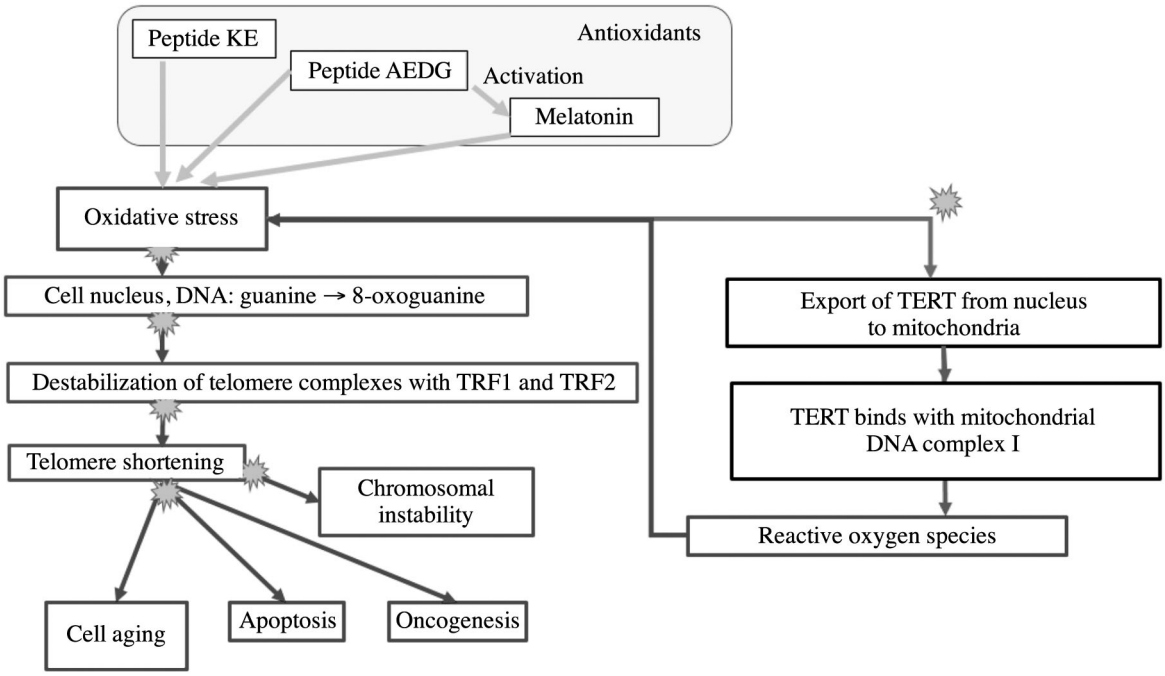

Fig. 4. Proposed mechanism of antioxidant and geroprotective actions of peptides AEDG and KE.

macrophages, lymphocytes, thymocytes, and neutrophils [2, 4, 9]. Administration of peptide KE into transgenic mice suppresses the expression of the HER-2/neu oncogene by a factor of two, which is accompanied by decreases in tumor diameter [4, 9]. In addition, peptide KE promotes increases in the proportion of transcribable euchromatin and decreases the quantity of heterochromatin in blood lymphocytes in elderly people [4].

The immune system peptide KE and the pineal peptide AEDG have been shown to regulate telomere length in PHA-stimulated blood lymphocytes. This result correlates with increases in longevity in animals given injections of these peptides. In most cases, changes in telomere length are seen in middle-aged people: eight cases in middle-aged men vs. four in young men. In addition, changes in telomere length were seen more frequently after administration of peptide AEDG (seven cases with statistically significant changes) than peptide KE (five cases). Increases in telomere length after use of study peptides were found twice as frequently than decreases: eight cases vs. four. The maximum increase in telomere length (by 156%) was recorded in PHA-stimulated lymphocytes from middle-aged humans after use of AEDG. Thus, a tendency to "normalization" of telomere length was seen in PHA-stimulated lymphocytes after exposure to peptides. Peptides AEDG and KE increased telomere length in lymphocytes as compared with the mean if it was below the mean and decreased it if it was initially greater than the mean [5, 6].

Peptide AEDG normalizes antioxidant activity in age-related pathology. Treatment with peptide AEDG increases antiradical activity against ROS as compared with its pre-treatment level [4]. There was also an increase in this activity as compared with a normal study group without pathology. In addition, peptides KE and AEDG decrease apoptosis and the quantity of ROS in rat neuron cultures. Addition of hydrogen peroxide to rat neuron cultures increased the quantity of ROS by a factor of eight. Addition of peptide KE to neuron cultures with hydrogen peroxide produced a statistically significant decrease in ROS by a factor of 0.8, while addition of peptide AEDG decreased it by a factor of 0.7 as compared with ROS in neuron cultures with hydrogen peroxide [31].

Thus, peptides KE and AEDG, which have antioxidant actions, decrease OS levels in cells. This promotes prevention of the subsequent cascade of reactions: transformation of guanine into 8-oxoguanine, destabilization of telomere complexes with proteins GRF1 and TRF2, telomere shortening, chromosomal instability, cell aging, apoptosis, and oncogenesis. In addition, the decrease in the level of oxidative stress in response to peptides breaks the positive feedback loop: oxidative stress – TERT export from the nucleus to mitochondria – binding of TERT to form a complex with mitochondrial DNA – oxidative stress (Fig. 4). This hypothesis is supported by the fact that the peptides are able to normalize telomere length and activate TERT, overcoming the limit of cell divisions.

Conclusions. OS is one of the mechanisms impairing the functions of cells, organs, and tissues on aging. Powerful OS whose sequelae cannot be eliminated by proteins of the antioxidant system damages DNA, RNA, protein, and lipid structures, leading to cell apoptosis. The elements most damaged by OS are neurons in the brain. Thus, age-related

diseases (AD, HC, PD, and others) can develop in conditions of OS. A potential direction in the treatment of neurodegenerative pathologies is provided by the use of antioxidants, for example melatonin or the short peptides AEDG and KE. Peptide AEDG stimulates endogenous melatonin synthesis in aging, while peptides AEDG and KE have antioxidant and geroprotective properties, normalizing telomere length and preventing cell apoptosis. An understanding of the molecular mechanisms of OS is important for supporting the physiological functions of the body in aging and neurodegenerative pathology.

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