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ВПЛИВ РАДІАЦІЇ НА ПРОЦЕСИ СТАРІННЯ ТА ДОВЖИНУ ТЕЛОМЕР

Теломери – кінцеві ділянки хромосом – це захисні «ковпачки», які забезпечують їхню стабільність. Вкорочення теломер є однією з найважливіших біологічних ознак старіння, причетне до процесів старіння клітин і задіяне у механізмах «мітотичного годинника». Пошкодження теломер вільними радикалами є одним із відомих механізмів впливу радіації на процеси старіння. А окислювальний стрес має токсичну дію на довжину теломер. Збільшення вільних радикалів відбувається під дією як іонізуючого, так і неіонізуючого випромінювання, хоча антиоксидантні механізми нерідко здатні нейтралізувати шкідливі вільні радикали. Неіонізуючі та іонізуючі випромінювання навіть у малих дозах спричиняють активацію антиоксидантних систем, однак при впливі на організм опромінення у високій дозі або протягом тривалого часу, чи то якщо в організмі відбуваються патологічні процеси з окислювальним стресом, пошкодження клітини стають більш виразними, а процеси старіння прискорюються. Підтримання довжини теломер і нормальної швидкості старіння є важливими для стану здоров'я. В огляді обговорюється роль іонізуючого та неіонізуючого випромінювання у процесах клітинного старіння, зокрема – у скороченні довжини теломер.

Ключові слова: старіння, радіація, окислювальний стрес, довжина теломер, токсичність.

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EFFECT OF RADIATION ON AGING PROCESSES AND TELOMERE LENGTH

Telomeres are the ending areas of chromosomes – protective «caps» that ensure the stability of chromosomes. Telomere shortening is one of the most important biological signs of aging and is involved in cellular aging and the «mitotic clock» mechanism. One of the known mechanisms of the impact of radiation on the aging process is damage to telomeres by free radicals. Oxidative stress has a toxic effect on telomere length. The increase in free radicals occurs under the action of both ionizing and non-ionizing radiation, although antioxidant mechanisms are often able to neutralize harmful free radicals. Low doses of non-ionizing and ionizing radiation even cause the activation of antioxidant systems, however, when the body is exposed to radiation at a high dose or for a long time, or if pathological processes with oxidative stress occur in the body, damage to cells becomes more noticeable, and aging processes accelerate. Maintaining telomere length and a normal rate of aging is important for health. In this review, we want to discuss the role of ionizing and non-ionizing radiation in cellular aging, in particular, in the shortening of telomere length.

Key words: aging, radiation, oxidative stress, telomere length, toxicity.

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BACKGROUND

Telomeres are the ending areas of chromosomes – protective caps that ensure the stability of chromosomes, in particular, with their protective function, they maintain genomic integrity and chromosomal stability [1].

Telomeres are made up of repeating sequences of nucleotides. Human telomeres are composed of a double-stranded G-rich tandem repeats followed by G-rich single-stranded overhangs at 3' ends [2]. The role of telomeres is to protect DNA from damage [3]. During somatic cell division, telomere length decreases due to the loss of nucleotides [4]. During replicative aging, telomere length is critically shortened and the risk of cell death is increased due to an increased hasard of mutations that cell try to avoid [5].

Telomere shortening is one of the most important biological signs of aging and is involved in cellular aging and the «mitotic clock» mechanism [6, 7]. Cell aging means aging of the body [8].

Various factors affect the natural shortening of telomeres: its shortening can be accelerated or slowed down by the action of some enzymes, substances or physical factors, e.g. by telomerase activity, cortisol action [9], stress, etc. [10].

Telomerase is an enzyme that maintains telomere length by slowing down telomere shortening by adding nucleotides to guanine-rich repeat sequences at the ends of chromosomes [11]. Therefore, telomerase activity is higher both under physiological conditions, for example, in germ cells, stem cells, and in pathologies – in tumor cells, when the precursor cell does not «age» by cell division, but, on the contrary, maintains immortality and the activity of the next reproduction [12]. In these cases, the cell activates mechanisms to maintain and protect the length of telomeres [13].

Accelerated aging occurs in various pathologies. Physical and mental factors also influence aging. Physical, emotional, psychological stress affects the length of telomeres, and hence the speed of the aging process [14, 15].

Shortening of telomeres is especially accelerated under the action of stress factors on a young cell or organism [16].

As already mentioned, the telomerase enzyme is involved in telomere shortening [17, 18], although this is not the only factor influencing the rate of telomere shortening. The role of oxidative stress in the physiology of cell aging is also important, and one of the common physical factors that alter the aging process by affecting oxidative and non-oxidative mechanisms is radiation [19].

It is known that damaging radiation causes various pathologies, such as cancer, mainly due to DNA damage. Due to these diseases, life expectancy is correspondingly reduced. Radiation also affects lifespan and aging processes [20]. Ionizing and non-ionizing radiation by different mechanisms cause shortening of the telomere length and, consequently, aging. These aging mechanisms depend on the radiation dose, duration of action, the state of the oxidative and antioxidant systems of the body, and many other factors [21]. Maintaining telomere length and a normal rate of aging is important for health. Rapid shortening of telomeres or, conversely, their elongation may be the cause of a pathological process or indicate various pathological conditions [22].

In this review, we want to discuss the role of ionizing and non-ionizing radiation in cellular aging, in particular, in the shortening of telomere length.

EFFECT OF RADIATION ON THE BIOLOGICAL PROCESSES OF AGING

Even in the last century, there was an opinion that radiation affected the aging process. In Paris, since 1933, the magic cream «To-Radia» was sold, which improved blood circulation and reduced wrinkles. This cosmetic product contained radioactive substances, including Radium [23]. In addition to cosmetic products, the radioactive energy drink «Radithor» was popular during this period, which killed many people. Today, everyone knows that radiation is dangerous to health, and its use to stop the aging process is clearly avoided.

To assess the biological processes of aging, the state of telomeres, oxidative and antioxidant systems and the risk of mutations (eg, chromosomal aberrations, the number of gene mutations, alteration in mRNA and protein levels and trans-generational effects) are measured [24].

Different doses of radiation and duration of action change these parameters differently, for example: after 400 days of irradiation at a dose of 1 mGy / day, changes in the incidence of neoplasms and chromosomal abnormalities were seen, while radiation of 0.05 mGy / day for 400 days significantly influenced mRNA data only [25].

It should be noted that in addition to the negative impact on the aging process, radiation can also have a positive effect [26]. A 2005 study in British radiologists and US nuclear workers found that low doses of radiation stimulate the body's immune system and link between radiation and cancer risk was found in this study [27].

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TELOMERE LENGTH AND AGING

Telomeres of somatic cells shorten as a result of repeated divisions. During each cell division, the telomere is shortened by an average of 50–200 bp [28].

Telomere length is longer in young body cells than in aging cells [29] (Fig. 1). So, telomere length is considered to be a determinant of cell age, i. e. the telomere length of human leukocytes is a marker of the biological age of a cell and, consequently, of an organism [30].

Considering that basically only so-called «immortal cells» (e.g. stem cells, germ cells, tumor cells, etc.) maintain or restore telomere length, telomere shortening or acceleration of somatic cell telomere shortening is usually an irreversible process in cell biology, which ultimately leads to cell death [31, 32].

Factors accelerating telomere aging are numerous: inflammatory mediators, CRP (C-reactive protein) [33, 34], depression [35], high levels of oxidized LDL (low density lipoprotein) [36], etc.

Epidemiological studies have confirmed the relationship between telomere length and age-related pathological conditions, for example, telomere length is relatively short in atherosclerosis [37], stroke stroke [38], type 2 diabetes mellitus [39], Parkinson's disease [40], etc.

Only 40–80 % of telomere aging is determined by genetic factors, i.e., their length is mainly determined genetically [41], although ultimately their lifespan largely depends on other, external and internal factors [42, 43].

Oxidative stress most affects telomere length [44]. Oxidative damage has a toxic effect on telomeres and causes their rapid shortening, while the effect of antioxidants, on the contrary, activates telomerase, which significantly reduces the rate of telomere shortening[45].

Accordingly, diseases whose pathophysiology is characterized by oxidative stress themselves affect the accelerated shortening of telomere length and, consequently, aging. e.g. diabetes mellitus, Alzheimer's disease, chronic lung diseases occur against the background of oxidative stress [46–49].

TELOMERE LENGTH CONTROL MECHANISMS

Telomere length is regulated by various proteins or by positive or negative control pathways [50, 51].

Telomerase, an enzyme elongates chromosomes by adding TTAGGG sequences to telomere, is present in low concentrations in somatic cells [52, 53].

The reason for this is that the aging of the somatic cell occurs at a normal rate, while its concentration is higher in the fetal and germ cells, that is, where the aging process proceeds very slowly. The concentration of telomerase is also high in tumor cells, where telomeres do not shorten during the multiplication of these cells, and, accordingly, aging in these cells decreases [54, 55].

One of the subunits of telomerase, reverse transcriptase (TERT), plays an important role in maintaining telomere length [56]. Telomerase activity through TERT expression ensures chromosome stability by maintaining telomere length, which in turn reduces cellular aging [57, 58].

In addition to intrinsic factors, extrinsic factors can also maintain telomere length [59], for example, in studies conducted on mice, the introduction of a number of vitamins (C, E), polyphenols, omega-3 and other nutrients with antioxidant and anti-inflammatory properties positively affects telomeres, i.e. reduces their shortening speed [60, 61].

Ribonucleoprotein telomerase is involved in telomere lengthening. It is especially active in non-somatic cells [62, 63]. Telomerase itself (in the case of humans) consists of two molecules: TERT, telomerase RNA (TR or TERC) and dyskerin (DKC1), therefore, telomerase activity is determined by these components [64].

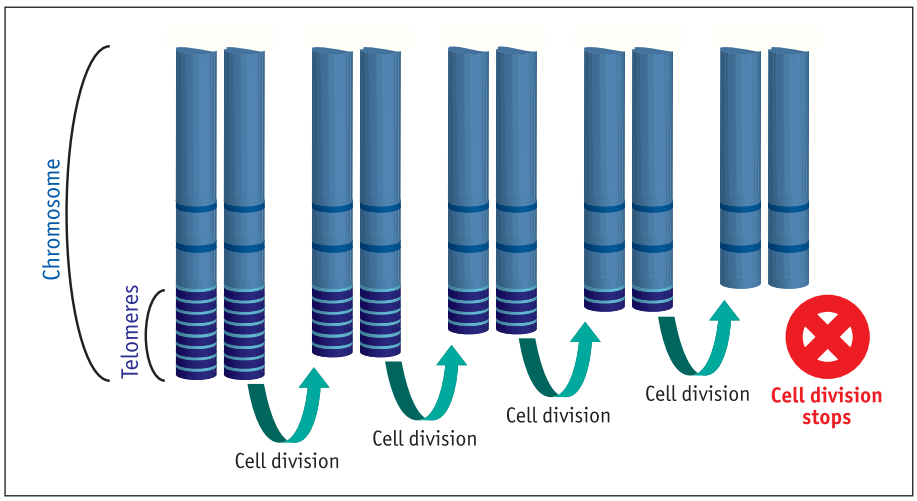

Figure 1. The telomere is shortened by an average of 50–200 bp. after each cell division. In the absence of telomeres, the cell stops dividing

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TERT

The addition of nucleotides, specific short repetitive DNA sequences to the nucleotide chain TTAGGG of the telomere at the ends of the chromosome is carried out using TERT, which leads to telomere lengthening and is controlled by the Shelterin complex [65].

The Shelterin complex, on the other hand, consists of six subunits of shelterin (TRF1, TRF2, TIN2, Rap1, TPP1, and POT1).

From Shelterin (also called telosome) proteins only TRF1 and TRF2 bind directly to duplex telomeric DNA and generate a T-loop to protect chromosome ends [66].

Telomerase RNA (TR or TERC)

Telomerase RNA is responsible for the correct architecture and structure of the telomerase complex [67]. It can function independently of telomerase, and its main function is to participate in catalysis, formation of autophagosomes, and localization, maturation, and assembly of telomerase [68].

THE ROLE OF OXIDATIVE SYSTEMS IN CELL AGING PROCESSES

We are talking about the aging of the cell and the organism as a whole, when it can no longer perform the corresponding function, therefore, the risk of death increases [69].

Endogenous and exogenous factors influencing the physiology of aging need to be considered separately. The reason for the acceleration of the natural aging process is mainly cell dysfunction [70].

There are many reasons for cell dysfunction, however, regardless of the physiological or pathological state, free radicals are actively involved in this process [71, 72]. In humans and mammals, oxygen is often involved in free radical reactions. If we can control free radicals, we will affect the aging process [73, 74].

The concentration of free radicals increases both in natural aging and in pathological conditions [75]. When free radicals are no longer regulated by the cell, oxidative stress develops.

This balance is restored through the activation and intervention of the antioxidant system [76].

Under the influence of antioxidants, it is possible to slow down the aging process both in natural and pathological conditions [77].

Free radicals pose a threat to organic and inorganic compounds, proteins, fats and DNA in the cell [78].

Oxidative systems are controlled by the body's antioxidant systems. Antioxidants are substances that reduce or neutralize oxidative processes and reactions. When oxidants cannot be neutralized and their amount is greater than that of antioxidants, oxidative stress develops [79, 80] (Fig. 2).

The cause of oxidative stress is the continuous generation of reactive oxygen species (ROS) and nitrogen (ROS), that is, an imbalance between the formation and detoxification of ROS and ROS [81].

It is possible to test the body's oxidative systems or antioxidant mechanisms using various biomarkers. For example, the level of oxidative stress is measured by the oxidative stress index (OSI). This is the ratio of total oxidative status (TOS) to total antioxidant status (TAS) [82, 83].

With age, TAS decreases and TOS and OSI increase, which means that oxidative stress increases with age [84].

To confirm the impact of oxidative stress on aging, the researchers analyzed the mortality risk score (MS) and found a statistically significant association between oxidative stress and MS at baseline [85].

Considering that oxidative systems work with defects during aging and antioxidant mechanisms are less able to participate in these reactions, it is logical that the risks of developing various diseases also increase [86].

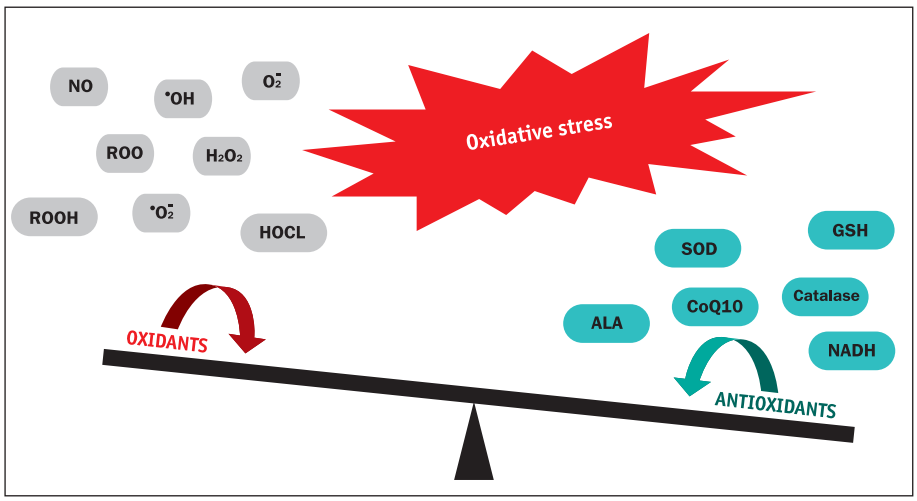

Figure 2. Antioxidants control the body's oxidative processes. If the oxidants cannot be neutralized, oxidative stress develops. Some of the oxidants are free radicals and cause cell damage through chain reactions.

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On the other hand, when a number of diseases occur with the involvement of antioxidant systems, this is already a double health risk, namely: changes caused by aging and pathological conditions further increase the risk of complications of these diseases. When the balance between reactive oxygen species (ROS) and antioxidant mechanisms is disturbed under oxidative stress [87], the aging process is accelerated and, accordingly, the risk of death increases [88].

Studies in mice showed that lifespan was not significantly affected by the shutdown of antioxidant defense systems, but when the mice in this group developed age-related pathologies, the disease progressed much faster than in the control group. Accordingly, it was concluded that minimal oxidative stress is not a factor affecting life expectancy, and chronic oxidative stress, on the contrary, accelerates the aging process and pathological complications [89].

EFFECT OF ACTIVITY OF OXIDATIVE SYSTEMS ON TELOMERE LENGTH

Telomere length changes over time and depends on the number of lost and restored nucleotides. The biological age of a cell is determined by the length of telomeres [90].

As is known, oxidative stress has a toxic effect on telomere length, namely exposure to ROS-generating agents and oxidative stress cause acceleration of telomere shortening in cells [91].

The exact mechanism by which telomere length is shortened during oxidative stress has not been elucidated, although there are several hypotheses.

The main cause of telomere shortening under oxidative stress is double-stranded DNA breakage during replication, which occurs when single-stranded DNA is damaged [92].

According to some versions, telomere shortening is caused by damage to the Shelterin complex during oxidative stress, and theories of the direct toxic effect of ROS on telomere nucleotides are also discussed [93, 94].

According to one version, if oxidative stress causes pathological reactions and cell death, intact cells are forced to compensate and divide more than was originally determined to maintain homeostasis. Consequently, with each division of the telomere, it loses nucleotides and shortens in length [95].

Shortening of telomeres is explained by a different mechanism of action, according to which ROS directly causes rupture and damage to one strand of the telomere [44, 96], while replication of this sequence no longer occurs and the telomere is shortened [97].

ANTIOXIDANT SYSTEMS AND CELL AGING

Oxygen has a high redox potential, so it is involved in a number of redox reactions. Some of these reactions can damage the cell by producing highly reactive particles [98], ex. reactive oxygen species (ROS) and reactive nitrogen species (RNS) [99]. These ROS and RNS can disrupt the redox balance inside cells. An imbalance between oxidants, antioxidants and biomolecules in the body can cause oxidative/nitrosative stress, namely hyperproduction/detoxification dysbalance [100–102].

Cells control the potential risks of ROS and RNS using different systems, i.e. [103], antioxidant enzymes (dismutase, catalase, glutathione peroxidase and thioredoxins), glutathione (GSH), uric acid, bilirubin, coenzyme Q10 and other substances regulate the level of oxidative stress through antioxidant mechanisms [104–108]. The ratio of glutathione to its oxidized form is one of the indicators of cellular redox level [109].

Antioxidant mechanisms neutralize the excess of free radicals [110], protect and repair oxidized membranes, ex. ?-tocopherol controls and protects cells membranes against damage caused by free radicals [111], they significantly reduce the rate of reduction of the concentration of peroxides [112], are involved in fat metabolism [113, 114].

Enhanced antioxidant systems have an «anti-aging» function [89, 115], Consequently, the weakening of antioxidant systems accelerates the aging process [116].

EFFECT OF IONIZING RADIATION ON THE OXIDATIVE AND ANTIOXIDANT SYSTEMS

At the cellular level, ionizing radiation directly and indirectly causes changes. Primary or chemical oxidative processes are followed by changes in secondary or biological processes [117].

To cope with redox stress, The body tries to fight radiation toxicity with quick reactions. With a large dose of radiation or prolonged exposure, the body is not able to resist and homeostasis is disturbed [118–120].

The main mechanism for changing cellular and extracellular substances by ionizing radiation is the radiolysis of water, followed by a chain of other chemical reactions, these changes extend to macromolecules and many cellular structures [121].

Radiolysis of water plays a major role in the formation of free radicals. In particular, as a result of these reactions is formed e^-aq, $\bullet OH$, $H\bullet$, H_2O_2, $O_2^{-}\bullet$, $HO_2\bullet$

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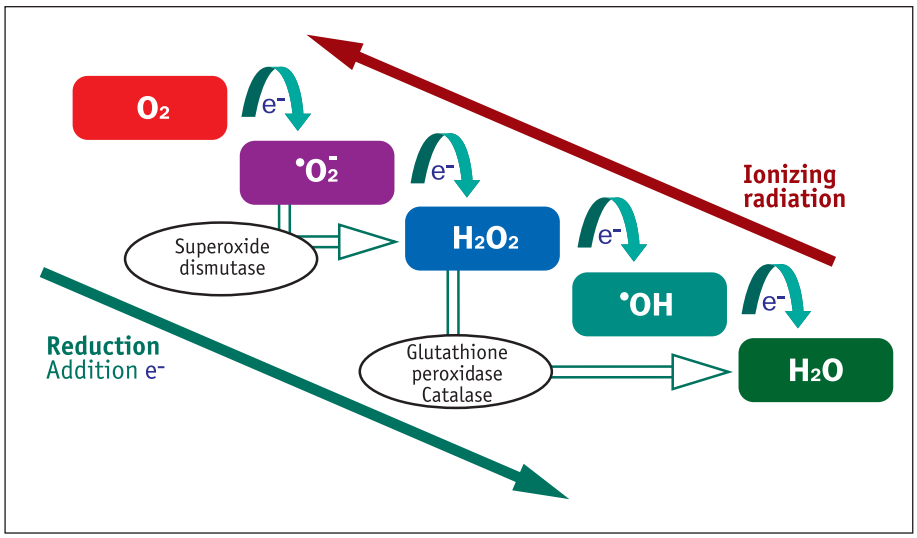

Figure 3. Radiolysis of water and radiation. Oxidants formed during the action of radiation increase the risk of oxidative stress.

radicals, which produces (itself) organic radicals (R•), peroxyl radicals (RO_2•), hydroperoxides (ROOH) and lipid peroxidation, protein inactivation occurs. These reactions are not limited to one cell. Through water or other chemical reactions, these processes are transmitted to other cells, ex. H_2O_2 and $O2^-$• can diffuse a longer distance away from the originating site and there they can enter into chemical reactions [122] (Fig. 3).

Radiation promotes the release of chemical agents responsible for oxidative and inflammatory stress [123].

Ionizing radiation stimulates the formation of nitric oxide (•NO), which reacts with $O2^-$• and forms peroxynitrite anion ($ONOO^-$), which, in turn, reacts with lipids, proteins and damages DNA. $ONOO^-$ oxidizes guanine (G), including in the telomere nucleotide chain (–TTAGGG–) [124–128].

Oxidation of one nucleotide of the guanine base gives 8-oxo-7,8-dihydroguanine (8-oxo-dG) (Fig. 4). This product of the oxidative reaction is also one of the biomarkers of aging [129]. In particular, as a result of the action of radiation, the oxidation of guanine leads to a combination with adenine instead of cytosine through Hoogsteen hydrogen bonding, which leads to mutations and instability of the genome in chronic or acute diseases such as cardiovascular disease, cancer, etc [130].

It is important to note that ionizing radiation not only causes rapid changes upon irradiation, but changes continue after irradiation, including in the cells of the next generation. In addition, from one irradiated cell, chemical reactions spread to other, non-irradiated cells and, accordingly, these reactions continue in their descendant cells, which increases the risk of mutations [131].

After the mutation, the cell tries to exclude the damaged fragment from replication, therefore, after reproduction, the telomere will shorten even faster, since the damaged chain of nucleotides does not replicate in it [132].

All cells respond differently to radiation, stress, including oxidative stress [133]. For example, in the case of nerve cells, large cells are more vulnerable, so age-related diseases such as Parkinson's disease or amyotrophic lateral sclerosis degeneration are more susceptible to oxidative stress, nerve cells die earlier, and health conditions become more complicated [134, 135].

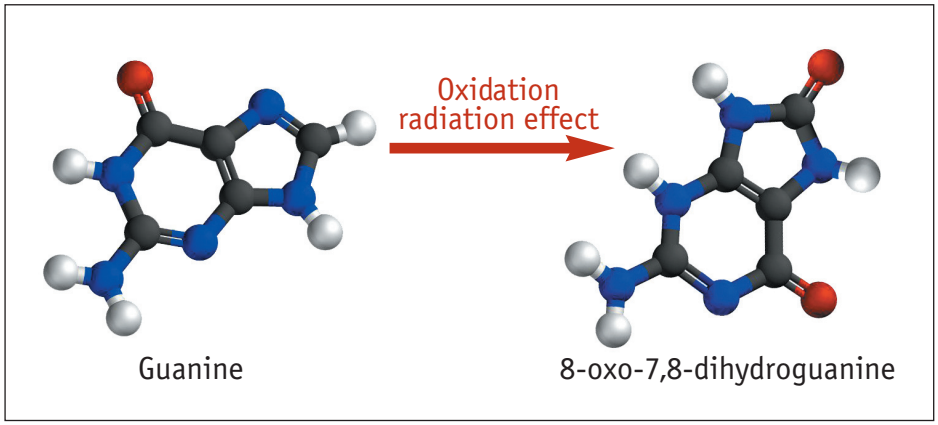

Figure 4. Under the action of radiation, guanine is oxidized to 8-oxo-7,8-dihydroguanine, which reacts with adenine in the nucleotide chain. This causes mutation and instability of the genome.

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And the hippocampal CA3 is more resistant to oxidative stress than CA1 neurons; therefore, aging processes in these neurons proceed more slowly [136].

It is true that different types and doses of radiation affect the body in different ways, but even small doses of ionizing radiation cause more oxidative stress [137, 138].

The level of oxidative stress caused by the action of radiation varies and depends on the linear energy transfer (LET) properties of the radiation. For example, short and long-term in vitro and in vivo effects are associated with mitochondrial DNA, mitochondrial protein import andmetabolic and antioxidant enzymes [139].

EFFECT OF NON-IONIZING RADIATION ON OXIDATIVE SYSTEMS

Ionizing radiation disrupts this balance by acting on the antioxidant and oxidizing systems of the cell. Oxidant-antioxidant balance is more easily disturbed in aged cells [140].

This imbalance is followed by a cascade of biological reactions, including accelerated cell aging, increased risk of mutations, etc [141].

Ionizing and non-ionizing radiation act on oxidative systems by different mechanisms. For example, if ionizing radiation mainly damages DNA, non-ionizing radiation greatly affects the body's antioxidant systems and oxidative repair mechanisms [142, 143].

It is true that both types of radiation result in the same damage to cellular structures, but the mechanism is different [144, 145].

In particular, by affecting the generation of reactive oxygen species (ROS), non-ionizing radiation affects the oxidative systems of the cell, which is due to the acceleration or reduction of biological processes and the toxic effect of metabolites or free radicals resulting from these processes [146].

Non-minizing radiation, namely exposure to a hypomagnetic field in mice causes significant impairments of adult hippocampal neurogenesis and hippocampus-dependent learning, which is strongly correlated with changes in ROS levels [147]. Under the action of ultraviolet rays, the concentration of ROS changes, affecting cellular components directly or through the mechanisms of photosensitization [148].

As with ionizing radiation, the bioeffects of non-ionizing radiation are dose and duration dependent.

In some cases, non-ionizing irradiation even leads to the activation of antioxidant systems [149], for example, in insect pests at UV in the range of 320–400 nm, exposure for 30 min led to an increase in total antioxidant capacity, peroxidases (POX) and glutathione-S-transferase (GST), and POX activity decreased after 60 and 90 minutes of exposure [150].

CONCLUSION

There are over 350 theories that explain the aging process.

Telomere length is considered one of the most reliable markers of aging.

Radiation causes many changes at the cellular level.

One of the known mechanisms of the impact of radiation on the aging process is damage to telomeres by free radicals. The increase in free radicals occurs under the action of both ionizing and non-ionizing radiation, although antioxidant mechanisms are often able to neutralize harmful free radicals.

Small doses of non-ionizing and ionizing radiation even cause the activation of antioxidant systems, however, when the body is exposed to radiation at a high dose or for a long time, or if pathological processes with oxidative stress occur in the body, damage to cells becomes more noticeable, and aging processes accelerate.

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Declaration of interest statement

The Authors declares that there is no conflict of interest.

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