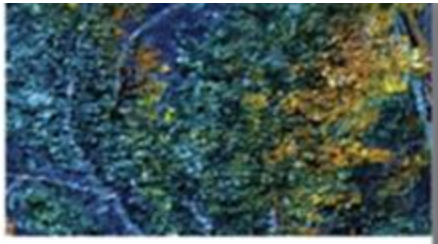

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CONTENT

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The Interplay between Mitochondria, MitomiRs, Radiation, and Age-Related Diseases: Prospects for Research

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Abstract: Aging is a complex biological process characterized by the gradual decline of cellular, tissue, and organ functions, ultimately contributing to the onset of age-associated diseases such as cardiovascular disorders, neurodegenerative conditions, and metabolic syndromes. Among the environmental factors influencing aging, radiation, particularly ionizing radiation, has emerged as a significant contributor to age-related deterioration. Despite advancements in understanding, the precise mechanisms by which radiation accelerates aging remain incompletely elucidated.

Recent research underscores the pivotal role of mitochondria and microRNAs (miRNAs), specifically mitomiRs, in mediating the effects of radiation on aging. Mitochondria, as the cellular energy powerhouses, are central to maintaining metabolic homeostasis and regulating cellular responses to stress. Radiation-induced alterations in miRNA expression profiles can disrupt these processes by impairing mitochondrial dynamics, biogenesis, and mitophagy. Additionally, radiation directly damages mitochondrial DNA (mtDNA) and mRNA, further compromising mitochondrial function. These changes not only accelerate the aging process but also increase susceptibility to age-associated diseases.

Age-related diseases, such as Alzheimer's disease, diabetes, and cancer, are strongly linked to mitochondrial dysfunction. Radiation exacerbates these conditions by amplifying oxidative stress, triggering inflammatory pathways, and impairing mitochondrial quality control mechanisms. Dysregulated mitomiRs play a dual role, acting both as mediators of damage and as potential biomarkers for identifying radiation-induced aging and disease progression.

This review consolidates existing evidence on the intricate interplay between radiation, miRNAs, mitochondria, and age-related diseases. It explores how radiation influences miRNA expression, mitochondrial health, and their combined effects on cellular metabolism and systemic aging. Understanding these interactions is crucial for identifying molecular targets and developing innovative strategies to mitigate radiation-induced damage. Novel therapeutic approaches, such as targeting key mitomiRs or enhancing mitochondrial resilience, hold promise for reducing the impact of radiation on aging and age-associated diseases, ultimately improving health outcomes in affected populations.

Keywords: aging, radiation, MitomiRs, mitochondrial dysfunction, age-related diseases.

Introduction

Aging is an inevitable and natural process in the life of organisms, characterized by the gradual deterioration of various organ and system functions. Understanding the mechanisms of aging is crucial for developing strategies to prevent and slow down this process. Previously, aging was perceived as an unavoidable and static outcome for cells. However, contemporary research allows us to understand that aging is a dynamic and multi-stage process.

The accumulation and persistent activity of senescent cells lead to disruptions in the microenvironment of aging tissues, influencing their function and contributing to the development of age-related pathologies. During cellular aging, cultured cells undergo a loss of proliferative capacity and adopt abnormal gene expression patterns. Various factors, including telomere shortening, DNA damage, and oncogene activation, can trigger the onset of aging. These triggers activate multiple mechanisms, from cell cycle arrest to the activation of tumor suppressors.

A prominent characteristic of aging cells is the stable cessation of their cell cycle. This cell cycle arrest is regulated through the activation of

pathways involving tumor suppressors like p53/p21 and p16. [1], both of which synchronize in the repression of CDK4/6. Typically, the INK4A/ARF locus is suppressed by repressive Polycomb complexes (PRC), but it becomes activated during aging. The p53/p21 CIP1 pathway is activated in response to DNA damage (DDR) from irreparable DNA lesions with chromatin alterations, thereby intensifying the aging process (DNA-SCARS) [2]. These pathways are considered barriers to malignant oncogenesis.

In contrast to quiescent cells, aging cells do not respond to mitogenic signals or growth factors, and hence, they cannot re-enter the cell cycle, even in a growth-permissive environment. Aging cells also differ from terminally differentiated cells, which also irreversibly exit the cell cycle.

Cellular growth arrest during aging is often triggered by a persistent response to DNA damage (DDR) induced by both endogenous factors such as oxidative damage, telomere exhaustion, and hyperproliferation, and exogenous factors like ultraviolet and gamma radiation, as well as chemotherapeutic agents, leading to a diminished intrinsic capacity of cells to undergo repair and restoration [3]. During replicative aging of human fibroblasts, there is a gradual shortening of telomeres, eventually resulting in the exposure of unreplicated free ends of double-stranded chromosomes. These exposed chromosome ends are recognized by the DNA damage response (DDR) mechanism as double-strand breaks [3]. When telomeres become critically short, the DNA repair system (DDR) is activated, which can lead to cellular aging and mitochondrial dysfunction [4].

Throughout the aging process, changes occur in genetic information, chromosomal structure, and protein homeostasis. For instance, an increase in genomic damage, epigenetic modifications, and disruptions in proteostasis (protein process balance) are observed in aging cells, tissues, and organisms. These alterations become more significant with age and can further accelerate the aging process [5].

These changes are regarded as common factors and phenotypes of aging, as they are observed during natural aging, and their experimental amplification accelerates aging, while their attenuation slows it down [6]. For example, genome damage, epigenetic changes, telomere shortening, and proteostasis disruption can mutually influence each other and contribute to the development of aging. Their coexistence and interaction can intensify aging processes and lead to more pronounced age-related alterations.

In addition to growth arrest, aging cells activate the production of various secreted factors known as the senescence-associated secretory phenotype (SASP). SASP is a complex set of signaling molecules that represents a key phenotypic program executed by senescent cells. One of the primary functions of SASP is to attract the immune system for the elimination of aging cells [7]. Moreover, SASP attracts immune cells, such as macrophages, neutrophils, and natural killer (NK) cells, which phagocytose and eliminate senescent cells. Secretion of various mediators and factors, including VEGF, can promote tissue remodeling by stimulating angiogenesis and reducing fibrosis. Lastly, the secretion of molecules like TGF-β can paracrinally propagate the aging phenotype to surrounding cells [8].

It has been found that with age, the risk of developing diseases such as Alzheimer's disease [9], Parkinson's disease [10], diabetes [11], cardiovascular diseases [12], chronic obstructive pulmonary disease (COPD) [13], osteoporosis, and osteoarthritis [14] increases. Statistical data indicate that around 100,000 people worldwide die daily from age-related causes [15].

Radiation contamination is a significant factor affecting the environment and human health. Typically, radiation is associated with an increased risk of developing malignant neoplasms [16]. However, several studies have demonstrated that radiation-induced damage triggers a senescence response at both the cellular and organismal levels [17,18]. According to Bertucci and colleagues, one of the presumed mechanisms of radiation-induced aging involves not only changes in DNA but also in the epigenome [19]. MicroRNAs (miRNAs) - small non-coding RNA molecules - are known to influence gene expression and participate in the epigenetic regulation of various physiological and pathological processes.

The expression profile of miRNAs is highly dynamic and sensitive to environmental factors. Several studies, including our own research group, have shown that radiation exposure, particularly to radon, can significantly impact the expression levels of these small non-coding molecules in humans [20,21,22].

Moreover, emerging evidence suggests an association between changes in miRNA profiles and age-related diseases [23]. Furthermore, experiments have shown that treatment of non-irradiated human fibroblasts with conditioned medium from irradiated cultures or exosomes isolated from irradiated medium leads to the development of a senescent phenotype in recipient cells [24]. Exosomes, secreted by almost all types of cells, predominantly contain miRNAs [25]. Thus, miRNAs are key regulators of aging processes and serve as sensors of adverse environmental factors, such as ionizing radiation.

Currently, multiple hypotheses have been proposed regarding the involvement of microRNAs (miRNAs) in the aging process. However, in the context of radiation-induced aging, the most promising targets for investigation are the group of mitochondrial microRNAs (mitomiRs). MitomiRs are microRNAs that regulate the expression of mitochondrial genes. Typically, mitoMIR genes have nuclear localization; however, there have been reports of a small number of microRNAs of mitochondrial origin [26].

This review consolidates existing evidence on the intricate interplay between radiation, miRNAs, mitochondria, and age-related diseases. It explores how radiation influences miRNA expression, mitochondrial health, and their combined effects on cellular metabolism and systemic aging. Understanding these interactions is crucial for identifying molecular targets and developing innovative strategies to mitigate radiation-induced damage. Novel therapeutic approaches, such as targeting key mitomiRs or enhancing mitochondrial resilience, hold promise for reducing the impact of radiation on aging and age-associated diseases, ultimately improving health outcomes in affected populations.

Aging and Mitochondria

In addition to the various factors mentioned earlier, disruption of mitochondrial homeostasis can also play a role in the onset of aging, contributing to accelerated age-related changes. As cells age, they accumulate molecular damage that can lead to dysfunction of various organelles, including mitochondria. This process is considered one of the factors promoting age-related changes and age-related diseases [27].

Patients suffering from various age-related diseases, such as chronic ischemic heart disease [28] and Alzheimer's disease [29], have been found to exhibit mutations in mitochondrial DNA. This suggests that mutations and alterations in mitochondrial DNA may play a role in the onset of aging.

Age-related mitochondrial dysfunction can be caused by several factors. One of them is the accumulation of mutations in mitochondrial DNA (mtDNA), which over time can negatively affect mitochondrial function. Another source of dysfunction is related to faulty mitochondrial proteins that play an essential role in metabolic processes inside mitochondria.

Studies show that mice with accelerated accumulation of mutations in mitochondrial DNA (mtDNA) age prematurely [30]. According to the data, these mice exhibit signs of aging at a younger age than usual. Conversely, the overexpression of mitochondrial-targeted catalase (mCAT), an enzyme responsible for protecting mitochondria, helps preserve their function and extends the lifespan of mice [31]. Thus, it is not surprising that aging and the senescence-associated secretory phenotype (SASP) respond to mitochondrial function within the cell in a similar manner. Mitochondria play a crucial role in both processes, and their dysfunction can lead to accelerated aging and the development of age-related pathologies.

Structural changes in mitochondrial membranes can also contribute to the occurrence of mitochondrial dysfunction. Mitochondrial DNA is more susceptible to damage from toxic chemicals compared to nuclear DNA [32]. This is due to the potential of the mitochondrial membrane, which creates a negative charge on the matrix side of the inner membrane. Imbalances in the processes of mitochondrial

fission and fusion can also play a role in aging and mitochondrial dysfunction. Additionally, insufficient mitophagy, the process responsible for removing damaged mitochondria, can lead to the accumulation of damaged organelles and, consequently, their dysfunction [6].

Mitochondria play a crucial role in cellular energy generation through the respiratory chain. During this respiratory chain process, mitochondria also produce oxygen radicals known as reactive oxygen species (ROS). Over time, the efficiency of the respiratory chain and electron transfer in mitochondria gradually decreases in organisms that utilize oxygen to sustain life [33]. This implies that with age, mitochondria become less efficient in energy generation, leading to the accumulation of dysfunctional mitochondria. According to the free radical theory, dysfunctional mitochondria can be a source of excess reactive oxygen species (ROS). These ROS can cause cellular damage and contribute to the aging process, affecting cellular components, including DNA, proteins, and lipids, leading to the accumulation of damage within cells, ultimately contributing to organismal aging. Moreover, reactive oxygen species (ROS) can also be generated due to external factors such as ultraviolet radiation and chemicals present in tobacco. These ROS can cause damage to cellular DNA, triggering a response similar to that caused by telomere shortening, known as DNA damage response (DDR). DDR involves the activation of factors such as p21 CIP1 and p16 INK4A [34], leading to accelerated aging.

Taken together, all these factors can contribute to the development of age-related mitochondrial dysfunction, which may be associated with various aspects of aging and the onset of age-related diseases.

Mitochondria and Age-Related Diseases

Recent studies have revealed a link between mitochondrial dysfunction and premature vascular aging, as well as the development of atherosclerosis. In one recent study, an analysis was conducted on the association of mitochondrial genetic variability with the severity of atherosclerosis in the carotid arteries and the presence of ischemic heart disease (IHD) [35]. Heteroplasmy for several mutations in mitochondrial DNA (mtDNA) in leukocytes showed a significant association with the severity of atherosclerosis in the carotid arteries and the presence of IHD. Specifically, mutations C3256T, T3336C, G12315A, G13513A, G14459A, G14846A, and G15059A were associated with the severity of atherosclerosis and the presence of IHD [36].

With aging, there is a progressive decrease in the expression of the protein Mfn2 (mitochondrial fission protein 2) in skeletal muscles. This contributes to the development of mitochondrial dysfunction, age-related metabolic disturbances, and sarcopenia (loss of muscle mass and function). Interestingly, reduced expression of Mfn1 and/or Mfn2 in skeletal muscles has been associated with the development of obesity and type 2 diabetes in both rodents and humans, indicating an important role of Mfn1 and Mfn2 in maintaining metabolic muscle function and their association with aging [37].

Furthermore, genetic defects in mitochondria can influence the development, plasticity, and function of the nervous system in neurodegenerative diseases. For instance, Alzheimer's disease, Parkinson's disease, and Huntington's disease have been associated with mitochondrial defects. These diseases are characterized by progressive degeneration of nerve cells and manifest various neurological symptoms [38].

In recent news, dysfunctional mitochondria have been found to negatively impact the body's immune response to viral infections, including COVID-19. Studies indicate that defective immune responses to viruses are associated with mitochondrial dysfunction, which can lead to a compromised ability of the body to combat the infection and an increased risk of severe COVID-19 outcomes [39].

The Impact of Radiation on Aging Mechanisms

In recent decades, mounting evidence suggests that radiation can influence the aging processes. However, it is crucial to note that the effects of radiation on the organism depend on various factors, including the dose, type of

radiation, duration of exposure, and the specific sensitivity of tissues and organs.

Ionizing radiation affects aging processes through molecular and cellular mechanisms. For instance, radiation-induced cell damage may contribute to carcinogenesis due to disruptions in cellular genetic material, leading to uncontrolled cell division and tumor formation. Cell death caused by radiation can result in tissue damage, and the loss of cells critical for normal organ and tissue function may lead to various pathologies. Consequently, molecular events induced by radiation may lead to non-specific reductions in lifespan [40].

Ionizing radiation can directly impact cells through cytological effects, with cell death being one of the most adverse outcomes [41].

Radiation exhibits multifaceted effects on stem cells (SCs), including their DNA repair capacity, cell cycle arrest, and activation of the senescence-associated secretory phenotype (SASP) [40]. The outcome of cellular repair of damaged DNA, determined by the accuracy of signaling pathways involved, is critical for determining cell fate, including senescence and apoptosis. DNA damage may lead to mutations and disruption of normal cell functions, which can have various consequences for the organism, including the development of cancer and other diseases. In cells incapable of repairing radiation-induced DNA damage, programmed cell death (PCD) is triggered, leading to cell demise [42]. Changes such as double-strand DNA breaks are considered potent stimuli for inducing aging processes.

Mitochondria in Radiation-Induced Aging

Several signaling pathways within mitochondria have been identified as inducers of cellular aging. Ionizing radiation causes long-term aging of endothelial cells by disrupting mitochondrial respiratory complex II function and generating superoxide. Mitochondrial oxidative stress, associated with mitochondrial dysfunction, plays a role in induced age-related immune senescence. MnTBAP (Mn (III) tetrakis (4-benzoic acid) porphyrin chloride) (SOD mimetic) and NAC (N-acetyl-L-cysteine) (ROS scavenger) have been shown to effectively reduce oxidative stress, sufficiently decreasing the percentage of senescence-associated β-galactosidase-positive aging endothelial cells. X-ray irradiation at doses ranging from 1 to 15 Gy leads to alterations in the mitochondrial network, characterized by decreased activity of respiratory complex II and increased superoxide production ($O2\cdot$), indicating mitochondrial dysfunction [43]. Prolonged endothelial cell aging is also associated with these changes, suggesting disruption of mitochondrial respiratory complex II and increased superoxide production. Thus, mitochondrial oxidative stress and dysfunction play a crucial role in immune senescence, and exposure to X-rays may exacerbate these processes, inducing alterations in the mitochondrial network and increased superoxide production.

Data indicate that UV radiation through mitochondria causes aging. One of the most studied damages is 8-oxoguanine (8-oxoG), which forms as a result of oxidative processes in cells and serves as a biochemical marker of UV-induced DNA damage [44].

Incorrect pairing of 8-oxoG with adenine during DNA replication leads to guanine being replaced by thymine, known as GC-to-TA transversion [45].

Early studies using high-performance liquid chromatography with electrochemical detection revealed that levels of 8-oxoG in mitochondrial DNA (mtDNA) are 16 times higher than in nuclear DNA (nDNA). This indicates a higher susceptibility of mtDNA to oxidative damage and may be associated with aging aspects.

Mechanisms of protection against UV-induced oxidative damage involve the removal of 8-oxoguanine-DNA (8-oxo-dG) through base excision repair (BER), and human 8-oxoguanine-DNA glycosylase (hOGG1) plays a crucial role in this process. HOGG1 specifically recognizes and breaks the glycosidic bond in the DNA strand, forming apurinic/apyrimidinic (AP) sites. Subsequently, missing nucleotides are restored with the assistance of DNA polymerase, and the gaps are sealed by DNA ligase. In HaCaT keratinocyte cells, inhibiting hOGG1 using microRNA (miRNA) was found to reduce repair of 8-oxo-dG induced by UV-A radiation [46].

MicroRNAs (miRNAs) have recently emerged as crucial regulators of gene expression.

They constitute a class of small RNA molecules that play a significant role in gene regulation. In the human genome, over a thousand miRNAs have been identified [47]. They act by binding to target mRNAs in a specialized region known as the 3'-untranslated region (3'-UTR). It is estimated that miRNAs regulate the activity of approximately 50% of all protein-coding genes in mammals [48].

Research has shown that miRNAs are involved in the regulation of almost all studied cellular processes, including cell growth regulation, programmed cell death (apoptosis), hematopoietic cell differentiation, and gene activity control [49].

Due to their stability and ease of measurement, miRNAs are considered reliable molecular markers for prognosis and diagnosis. Dysregulation of miRNAs is implicated in the pathogenesis of various conditions, ranging from cancer to autoimmune and cardiovascular diseases [50].

MiRNAs are also associated with inflammatory processes, heart and vascular diseases, autoimmune diseases such as rheumatoid arthritis, and infectious diseases, including viral and bacterial infections [51].

Moreover, miRNAs serve as biomarkers in liver diseases [52], cardiovascular diseases [53], lung diseases [54], and cancer [55].

Numerous studies have reported that miRNAs are non-invasive or minimally invasive biomarkers present not only in solid tissues but also in various body fluids [56]. Weber determined the abundance of miRNAs in 12 types of body fluids. Some miRNAs with high content (e.g., miR-509-5p, miR-515-3p, and miR-335) were distributed in different body fluid types, suggesting that these miRNAs may have a common function or origin. Based on currently detectable miRNA expression profiles, certain miRNAs were found to be present only in specific body fluid types, such as miR-224 in plasma, miR-637 in tear fluid, miR-193b in breast milk, and miR-508-5p in sperm [57].

Radiation and its impact on microRNAs

MicroRNAs (miRNAs) have garnered interest in the field of ionizing radiation as molecules responsive to radiation, prompting researchers to explore their potential as biomarkers for tumor radiation response and predicting radiation toxicity in normal tissues [22].

Ionizing radiation inflicts serious damage to cells, causing stress and disturbances in their functioning. This damage can occur directly through the disruption of DNA by the energy of radiation or indirectly by the generation of free radicals within cells [58].

Several studies have shown alterations in miRNA expression profiles following exposure to various types of radiation, including X-rays, gamma rays, as well as alpha and beta particles. It is important to note that changes in miRNA expression profiles may be transient and dependent on the radiation dose and type, as well as the tissue type or cell line under investigation in the study. Some miRNAs may be upregulated immediately after radiation exposure, while others may exhibit changes in expression at later stages.

It has been found that miRNA expression is influenced by proinflammatory signals, changes in osmolarity, stress experienced by cardiomyocytes in heart failure, and certain miRNAs have been found to be localized in stress response elements in cells exposed to various stressors [59].

Studies have been conducted to investigate how radiation exposure affects miRNA expression in different animal species. Among them, mice are a well-characterized species and the most commonly used animal model to study the consequences of radiation exposure.

Changes in microRNA expression upon ionizing radiation are part of a broader process occurring in cells in response to DNA damage or oxidative stress. Previous studies have confirmed that specific types of microRNAs are associated with DNA repair processes. For instance, microRNAs miR-17 and miR-20a have been shown to influence the regulation of the G1 checkpoint by targeting the transcription factor E2F1 [60]. This implies that these microRNAs can control the transition of cells from the G1 phase to the subsequent stages of the cell cycle. Additionally, microRNA miR-34 is known to regulate the activity of the p53 protein, which plays a key role in DNA repair control and the suppression of cancer growth.

However, it is important to note that not all miRNAs activated or suppressed during aging play a decisive role in the aging process. To provide direct evidence of the role of specific miRNAs in aging regulation, functional studies such as miRNA knockouts or overexpression are required. These studies will establish a direct cause-and-effect relationship between specific miRNAs and the aging process.

MicroRNAs that regulate mitochondria

So far, miRNAs have been detected in the nucleus and in multivesicular bodies in humans. It has been reported that pre-miRNAs and mature miRNAs are also present in mitochondria, expanding the potential for mitochondrial miRNA synthesis. Recently, microRNAs have also been identified in mitochondria isolated from rat liver, and they are believed to originate from mitochondrial DNA. They play an important role in the normal functioning of mitochondria, regulating both mitochondrial genes and the expression of nuclear transcripts related to mitochondrial processes. This family of regulatory molecules is known as mitomiRs [61].

Bandiera and colleagues [62] investigated a total of 57 miRNAs that were differentially expressed in mitochondrial and cytosolic fractions. These miRNAs are capable of directly influencing the regulation of mitochondrial genes and mitochondrial activity.

Research on MitomiRs is still in its early stages, and their precise functions and mechanisms of action are still being studied. However, it is known that MitomiRs can influence bioenergetic metabolism, apoptosis (programmed cell death), and other processes within mitochondria. They perform regulatory functions by controlling the activation of oncogenes and tumor suppressor genes, which affect the process of carcinogenesis [63].

Some studies indicate that radiation can alter the expression profile of MitomiRs. This suggests that radiation can influence the quantity and types of mitochondrial mi-croRNAs produced in cells. Changes in the expression profile of MitomiRs can affect mitochondrial functions and metabolic processes within cells.

MicroRNAs and age-related diseases

Altered functions of aging cells can have harmful effects on the organism, acceler-ating the aging process and/or leading to the loss of cells in various tissues. This, in turn, results in reduced organism functionality and increased risk of age-related diseases [64].

Some microRNAs, such as let-7, miR-17, and miR-34, are particularly important when considering long-lived individuals and the onset of age-related diseases. Long-lived individuals exhibit reduced expression levels of these microRNAs, which may be associated with molecular mechanisms promoting longevity and protecting the organism from age-related changes. However, in some age-related diseases, such as cancer and cardiovascular diseases, the activation of miRNAs let-7, miR-17, and miR-34 occurs [65]. The activation of these microRNAs may influence the expression of genes involved in cell proliferation, inflammation, apoptosis, and other processes relevant to the development of cancer and cardiovascular diseases.

Certain microRNAs are specific to cells and tissues [66]. Studies show that miR-132 plays a key role in regulating neuron maturation and the formation of their structures, thus participating in the formation of complex neuronal networks and connections be-tween neurons. It is presumed that disruption of miR-132 regulation in the mature nervous system may play a role in the development of certain neurocognitive disorders such as Alzheimer's disease [67].

MicroRNAs may also play a significant role in the pathological mechanisms associ-ated with diabetes and glucose level disorders. In one study, the expression of serum microRNAs related to diabetes (miR-9, miR-29a, miR-30d, miR-34a, miR-124a, miR-146a, and miR-375) was analyzed in patients with glucose level disorders [68]. MiR-34a, in particular, showed the most significant changes in expression, suggesting its crucial role in the development and progression of diabetes.

Furthermore, research indicates that age-related diseases may be associated with changes in the expression of circulating microRNAs in body fluids such as serum and plasma. MicroRNAs can be released upon tissue damage or shed from the plasma membranes of various

cell types. They exhibit remarkable stability and resistance to various external factors, such as heating, pH changes, prolonged storage, and freeze-thaw cycles [69]. These microRNA features make them attractive as potential biomarkers of age-related diseases.

Studies have shown that miR-206 and miR-567 may be associated with the devel-opment of neurodegenerative diseases, including dementia [70]. They may play a decisive role in regulating neuronal differentiation, maintenance of their function, and survival. The introduction of these microRNAs as biomarkers allows the assessment of changes in their expression and their use as indicators of the presence of mild cognitive impairment (MCI) and early stages of dementia. They can help determine the risk of developing dementia, as well as assess treatment effectiveness and predict disease progression.

Conclusions

Aging is a natural process accompanied by gradual deterioration of organism func-tions and an increased risk of various age-related diseases. This is associated with the impaired function of aging cells. Diseases such as cardiovascular diseases, diabetes, cancer, neurodegenerative disorders, and others are linked to age-related changes and accelerated organism aging, where mitochondria, mitomiRs, and radiation play signifi-cant roles. Understanding the mechanisms related to the altered function of aging cells can aid in the development of prevention and treatment strategies for age-related diseases.

Recent studies show that radiation can have a significant impact on the aging pro-cess. Mitochondria, known as the "powerhouses" of the cell, play a key role in metabolism, energy supply, and the regulation of cellular aging. They have their own DNA and repair mechanisms, but when exposed to radiation, mitochondria can be damaged, leading to dysfunction and accelerated cellular aging.

Interestingly, certain microRNAs, such as miR-21, miR-125a, miR-22, and miR-29b, have been identified as important players in the link between radiation, aging, and mi-tochondria. For instance, studies show that miR-21 can be upregulated in hippocampal cells and brain tissue following ionizing radiation exposure and also participate in mus-cle regeneration and regulation of genes related to mitochondrial function.

Understanding the interplay between mitochondria, mitomiRs, radiation, and age-associated diseases is crucial for developing strategies to protect the organism from the harmful effects of radiation and finding new approaches to slow down aging.

Further research should be directed towards a deeper understanding of the specific mechanisms through which radiation affects microRNAs and mitochondria, as well as the development of potential molecular targets and therapeutic approaches to prevent or mitigate the negative consequences of radiation on aging.

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Митохондриялар, митоМИР, радиация және жасқа байланысты аурулар арасындағы өзара әрекеттесу: зерттеу перспективалары

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Аңдатпа. Қартаю – бұл күрделі биологиялық процесс, ол жасушалардың, тіндердің және мүшелердің қызметінің біртіндеп төмендеуімен сипатталады, бұл жүрек-қан тамырлары аурулары, нейродегенеративті бұзылыстар және метаболикалық синдромдар сияқты жасқа байланысты аурулардың дамуына ықпал етеді. Қоршаған орта факторларының ішінде қартаюға әсер ететін иондаушы радиация жасқа байланысты өзгерістердің маңызды катализаторы ретінде ерекшеленеді. Алайда, радиацияның қартаюды жеделдету механизмдері әлі де толық зерттелмеген.
Қазіргі зерттеулер радиацияның қартаюға әсерін іске асыруда митохондрия мен микроРНҚ (миРНҚ), әсіресе митомиРНҚ маңызды рөл атқаратынына назар аударады. Клетканың негізгі энергия көзі болып табылатын митохондриялар метаболикалық теңгерімді қолдау және жасушалық күйзелістерге жауап беру үшін өте маңызды. Радиация миРНҚ экспрессиясының профильдерін өзгертіп, митохондриялық динамиканы, биогенезді және митофагияны бұза алады. Сонымен қатар, иондаушы радиация митохондриялық ДНҚ мен мРНҚ-ны тікелей зақымдап, митохондриялардың дисфункциясын күшейтеді. Бұл өзгерістер қартаюды жеделдетіп қана қоймай, жасқа байланысты аурулардың даму қаупін арттырады.
Альцгеймер ауруы, қант диабеті және онкологиялық аурулар сияқты жасқа байланысты патологиялар митохондрия жұмысының бұзылуымен тығыз байланысты. Радиация бұл аурулардың дамуын күшейтеді, тотығу күйзелісін арттырады, қабыну процестерін белсендіреді және митохондрия сапасын бақылау жүйелерін бұзады. Бұл жағдайда өзгерген митомиРНҚ екі жақты рөл атқарады: олар зақымдануды реттейтін факторлар ретінде және радиацияның қартаю мен аурулардың өршуіне әсерін көрсететін әлеуетті биомаркерлер ретінде әрекет етеді.
Бұл шолуда радиация, миРНҚ, митохондрия және жасқа байланысты аурулар арасындағы байланыстар туралы өзекті мәліметтер ұсынылған. Радиацияның миРНҚ экспрессиясына, митохондрия жағдайына және олардың жүйелі қартаюдағы рөліне қалай әсер ететіні қарастырылады. Бұл күрделі өзара әрекеттесулерді түсіну молекулалық нысандарды іздеу және радиациядан туындаған зиянды азайту бойынша инновациялық тәсілдерді әзірлеу үшін өте маңызды. Болашақта негізгі митомиРНҚ-ға мақсатты әсер ету немесе митохондрияның тұрақтылығын арттыру радиацияның қартаюға және жасқа байланысты ауруларға әсерін төмендетуге арналған тиімді стратегиялардың негізі бола алады, бұл зардап шеккен халық топтарының денсаулығы мен өмір сүру сапасын жақсартуға мүмкіндік береді.
Түйін сөздер: қартаю, радиация, митомиРНҚ, митохондриялық дисфункция, жасқа байланысты аурулар

Взаимодействие митохондрий, митоМИР, радиации и возрастных заболеваний: перспективы исследований

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Аннотация. Старение — это сложный биологический процесс, сопровождающийся постепенным снижением функциональной активности клеток, тканей и органов, что способствует развитию возрастных заболеваний, таких как сердечно-сосудистые патологии, нейродегенеративные расстройства и метаболические синдромы. Среди факторов окружающей среды, влияющих на процессы старения, ионизирующая радиация выделяется как один из значимых катализаторов возрастных изменений. Однако механизмы, посредством которых радиация ускоряет старение, до сих пор остаются недостаточно изученными.
Современные исследования акцентируют внимание на важной роли митохондрий и микроРНК (миРНК), особенно митомиРНК, в реализации эффектов радиации на старение. Митохондрии, будучи основными поставщиками энергии для клеток, критически важны для поддержания метаболического баланса и реагирования на клеточный стресс. Радиация способна изменять

профили экспрессии миРНК, нарушая тем самым митохондриальную динамику, процессы биогенеза и митофагии. Кроме того, ионизирующее излучение напрямую повреждает митохондриальную ДНК и мРНК, что усугубляет дисфункцию митохондрий. Эти изменения не только ускоряют старение, но и увеличивают риск развития возрастных заболеваний.

Возрастные патологии, включая болезнь Альцгеймера, диабет и онкологические заболевания, тесно связаны с нарушением работы митохондрий. Радиация усугубляет их развитие, усиливая окислительный стресс, активируя воспалительные процессы и подрывая системы контроля качества митохондрий. При этом измененные митомиРНК выполняют двойственную функцию: они выступают как регуляторы повреждений и как потенциальные биомаркеры, отражающие влияние радиации на старение и прогрессирование болезней.

В данном обзоре представлены актуальные данные о взаимосвязи между радиацией, миРНК, митохондриями и возрастными заболеваниями. Рассматриваются механизмы, посредством которых радиация влияет на экспрессию миРНК, состояние митохондрий и их роль в системном старении. Осмысление этих сложных взаимодействий имеет ключевое значение для поиска молекулярных мишеней и разработки инновационных подходов к снижению вреда, вызванного радиацией. В перспективе, целенаправленное воздействие на ключевые митомиРНК или усиление митохондриальной устойчивости может стать основой для эффективных стратегий борьбы с радиационно-индуцированным старением и возрастными заболеваниями, улучшая здоровье и качество жизни пострадавших групп населения.

Ключевые слова: старение, радиация, митомиРНК, митохондриальная дисфункция, возрастные заболевания.