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MitomiRs: The Role of Mitochondrial miRNAs in Regulating Radiation-Induced Cellular Senescence

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Abstract. The problem of human exposure to ionizing radiation has attracted increasing attention in various scientific fields. Recently, a substantial amount of data has been collected on the age-related risks associated with radiation exposure, which has enabled researchers to uncover the relationship between ionizing radiation and cellular senescence. This has led to the search for cellular targets of radiation, with mitochondria being one of the identified targets. Ionizing radiation causes mitochondrial dysfunction and the emergence of a characteristic age-related phenotype in cells, including increased ROS production, SASP development, changes in the epigenetic profile, and genomic instability. Mitochondrial dysfunction is often underestimated as a crucial hallmark of cellular senescence, and its underlying mechanisms are extensive and complex. In particular, mitochondrial miRNAs (mitomiRs) that regulate mitochondrial gene expression, and consequently, the function and dynamics of the organelles themselves, are of particular interest. Considering that mitomiRs are highly sensitive to even minor disturbances arising from irradiation, resulting in significant changes in their expression, they may serve as promising biomarkers of radiation exposure. In this review, we examine the evidence supporting the key role of mitomiRs in radiation-induced cellular senescence and integrate the latest knowledge on the underlying molecular mechanisms of this interaction.

Keywords: cellular senescence, ionizing radiation, mitochondria, mitomiRs, mitochondrial dysfunction, SASP.

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Introduction

Questions regarding the mechanisms of organism aging and the possibility of its slowing down have been of interest to the scientific community for several decades. Considering that the solution to complex processes often lies in details, the cellular theory of aging was proposed at the end of the 20th century [1]. The paradigm of the proposed theory is that, by studying the mechanisms of aging of individual cells, one can obtain an idea of the aging process of the organism as a whole. In the following years, the cellular theory of aging has been widely recognized and is now generally accepted [2–4]. In scientific literature, the term “cellular aging” or “senescence” is defined as an irreversible cell cycle arrest occurring in response to various stressors and acquiring a characteristic secretory phenotype [5].

The concept of the exposome, which encompasses the effects of the environment on an individual throughout its lifespan, is of great importance in senescence [6,7]. For the most part, it concerns the interaction between the (epi)genome and individual components of the exposome, such as ionizing radiation, UV irradiation, and toxins [7,8]. Recently, environmental radiation pollution has garnered considerable attention due to the extensive utilization of ionizing radiation across diverse aspects of life. People are exposed to radiation in various ways, ranging from natural sources of exposure [9] to industry [10], as well as a broad spectrum of medical procedures that involve the use of X-rays [11,12].

The effects of ionizing radiation on cells can vary depending on factors such as the dose, power, LET, and duration of irradiation Sometimes, cellular response mechanisms can mitigate the negative consequences of radiation exposure. On other occasions, however, they may result in apoptosis or senescence [13]. Double-strand breaks (DSBs) in DNA are the most destructive effect of radiation. Ionizing radiation can cause DSBs directly or indirectly by generating reactive oxygen species (ROS) and causing mitochondrial dysfunction [14].

MiRNAs are significantly involved in the response to DNA damage, cell death, and tumor aggression [15–18]. The main role of these small non-coding RNA molecules in organisms is the regulation of target genes expression [19]. Although miRNAs are commonly thought of as repressors that "switch off" target genes, it is important to recognize that they can also function as activators, promoting their targets [20]. Multiple miRNAs can enhance or repress translation depending on the state of the cell cycle [20,21]. The regulatory network that determines the relationship between miRNAs and mRNAs is complex and multifaceted. On the one hand, a miRNA can influence the functionality of one or several mRNAs. Conversely, the expression of mRNA transcript can be modulated by many different miRNAs [22]. This flexibility of the interaction system makes it possible to regulate biological processes on a large scale.

As noted earlier, ionizing radiation poses a threat to genome integrity. Given the inherent role of miRNAs as regulators, it is reasonable to assume that they are also involved in cellular response to radiation. However, the involvement of specific miRNAs remains unclear. Much of the available data indicate differential expression of miRNAs under the influence of ionizing radiation [23]. By employing high-throughput technologies such as sequencing, PCR-RT, and others, certain miRNAs have been identified with altered expression levels following irradiation

[16,24]. Although the scientific community has a wealth of knowledge about miRNAs, there is still incomplete information regarding their radiosensitivity and radioresistance. Researchers are still working on identifying particular miRNAs that show significant changes due to radiation exposure, with the aim of utilizing them to monitor the consequences of ionizing radiation.

In this review, we discuss promising mitochondrial miRNAs associated with radiation-induced cellular senescence. We hope that our findings, along with future studies examining the mechanisms of radiation-induced changes in mitochondrial function and miRNAs, will significantly contribute to the development of senotherapy and therapeutic approaches for mitigating the harmful effects of radiation exposure.

1. The Mitochondrial Basis of Cellular Senescence

The history of studying the role of mitochondria in cellular senescence processes began with the Free Radical Theory of Aging (FRTA). According to FRTA, aging is mediated by the accumulation of cellular damage initiated by free radicals [25]. Therefore, scientists have focused their attention on mitochondria, the main source of ROS [26]. Currently, the significance of FRTA is being called into question, and various interpretations of ROS's function in the aging process are being developed. ROS serves as essential signaling molecules that relay information to cells about potential danger and enable them to respond to stress [27]. However, excessive accumulation of ROS leads to molecular damage and oxidative stress, which is characterized by an imbalance between excessive ROS production and the ability of the cell's antioxidant system to cope with it [8].

Thus, the idea of FRTA in its pristine form, although disputed, once served as a solid foundation for studying the relationship between mitochondria and senescence. Over the past few years, the concept of the negative role of ROS has been revised and presented based on the gradual response hypothesis [28]. ROS is thought to function as a stress signal in response to age-related damage, indicating elevated levels of free radicals as a result rather than a cause of aging. However, excess ROS can exceed the antioxidant capacity of the cell, provoking oxidative damage, and ultimately contributing to age-related genomic instability [27,28]. This duality of ROS is well demonstrated by the influence of exposome components [8]. In addition to intracellular sources, oxidants are actively formed because of external triggers, particularly radiation. The connection between the indirect negative effects of ionizing radiation and oxidative stress in irradiated cells is closely intertwined with the process of radiolysis of water, which promotes the increased formation of intracellular ROS [29].

In addition to the impaired antioxidant system and increased ROS levels, the mitochondria's involvement in cellular senescence is also attributed to their own genome [30,31]. Mitochondrial DNA (mtDNA) is a vulnerable target of both exogenous and endogenous factors. Accumulation of mtDNA mutations leads to changes in mitochondrial biogenesis and dysfunction, which in turn initiate premature cellular senescence and the manifestation of an age-related phenotype [32–35] Changes in the number of mtDNA copies have been proposed as biomarkers of

mitochondrial dysfunction in response to ionizing radiation [36]. Senescent cells have increased levels of cytosolic mtDNA [37] and a high frequency of mtDNA mutations [38].

The release of mtDNA under conditions of metabolic stress leads to activation of the cGAS-STING pathway, mediating the development of the senescence-associated secretory phenotype (SASP) [39]. Senescent cells produce numerous signalling molecules in their microenvironment, including proinflammatory cytokines, chemokines, growth factors, and proteases, the most extensively considered of which are IL-1α, IL-1β, IL-6, IL-8, TNF-α, and MMP-1. The association of these molecules represents a major component of SASPs that contributes to the maintenance of cellular senescence [40]. Additionally, higher levels of ROS [31] and DNA damage can trigger the activation of the NF-kB family of transcription factors, which play a significant role in responding to stress and regulating a vast array of genes [41]. NF-kB, along with cGAS-STING, acts as one of the main inducers of SASP [42]. Interestingly, treatment of senescent cells with antioxidants decreases ROS levels and inhibits NF-kB pathway activation; however, direct inactivation of NF-kB has no effect on ROS production [43].

Furthermore, mitochondrial dysfunction triggers the onset of a specific type of cellular senescence known as mitochondrial dysfunction-associated senescence (MiDAS). The signs of MiDAS in senescent cells are typically related to a decrease in the NAD+/NADH coenzyme ratio, rather than mtDNA or ROS, which leads to the activation of AMP-activated protein kinase (AMPK) [44]. Similarly, AMPK activation, increased ROS, increased mitochondrial mass and mtDNA were demonstrated in a study on the manifestation of stress-induced cellular senescence [45]. Mitochondrial metabolism is highly dependent on the NAD+/NADH ratio [46,47]. Disruption of mitochondrial metabolism can have serious consequences, including interference with epigenetic regulation. The interaction of mitochondria with epigenetic markers can also be disturbed by environmental pollutants [46]. Interestingly, the aryl hydrocarbon receptor (AhR) was recently proposed as a model of the “exposome receptor”. AhR activation has been reported to occur in response to exposure to environmental pollutants, initiating a range of toxic events through mitochondrial dysfunction [46]. AhR is involved in many physiological processes, including pathological conditions, through epigenetic mechanisms involving miRNAs. AhR-dependent expression of miRNAs depends on cell type, ligand, and other aspects [48]. A protective function of AhR in the context of oxidative DNA damage through its agonist β-naphthoflavone (BNF) has been observed without affecting ROS levels in cells. Exposure to ionizing radiation leads to AhR activation [49], and the suppression of apoptosis and cell cycle arrest in a BNF-dependent manner [50].

These and other observations confirm the existence of a strong relationship between mitochondria and cellular senescence (Figure 1). This relationship was further confirmed by experiments in which mitochondria-depleted cells exposed to various senescence-inducing stressors (i - X-ray irradiation, ii - oxidative stress, iii - oncogene-induced senescence, and iv - replicative senescence) showed a decrease in the level of ROS, SASP factors, and other signs of senescence phenotype [51].

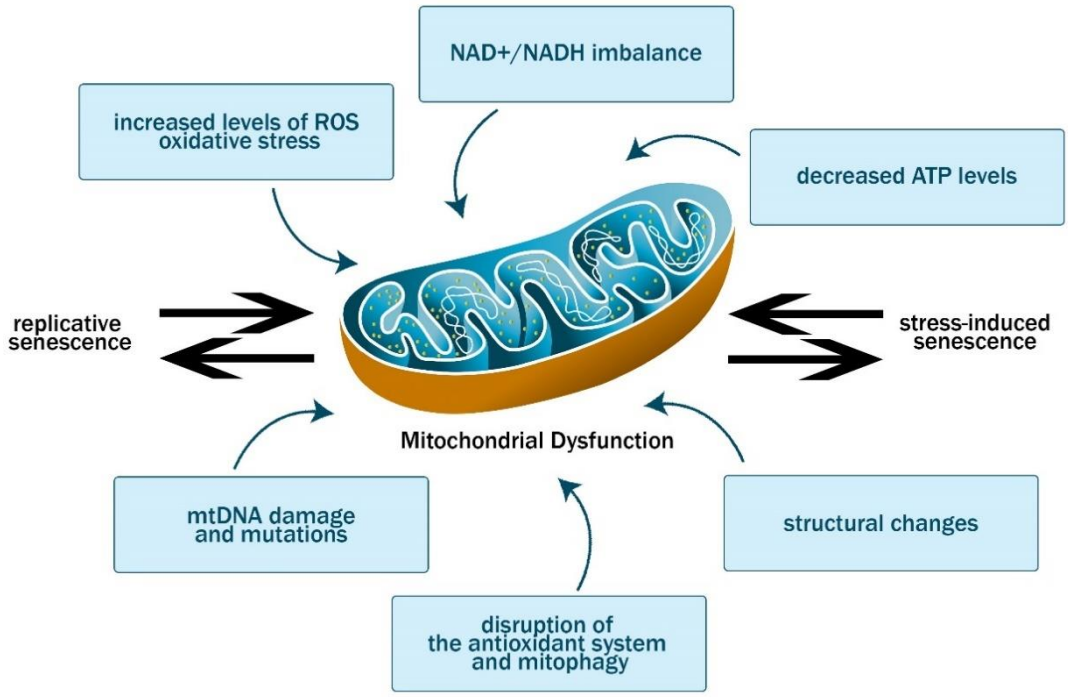

Figure 1. Relationship between mitochondrial dysfunction and cellular senescence

The mitochondria in senescent cells show several changes in terms of function, structure, and dynamics. Oxidative stress, damage and accumulation of mitochondrial DNA (mtDNA) mutations, impaired antioxidant systems, and mitophagy have been observed in senescent cells. Structural changes are mediated by the elongation of mitochondria and an increase in their total mass. Adenosine 5′-triphosphate (ATP) levels are reduced, there is an imbalance in the NAD+/NADH ratio, and excessive production of reactive oxygen species (ROS) is demonstrated.

2. Mitochondrial miRNAs in Cellular Senescence

The previously presented data indicate the extensive involvement of miRNAs in the regulation of multiple cellular processes, including the intriguing relationship of the “exposomal receptor” AhR with epigenetic mechanism [48], as well as the influence of redoximiRs on the expression of genes responsible for ROS generation and antioxidant defence [8,52,53]. Previous research, including ours, has demonstrated that exposure to ecotoxicants triggers a variety of cytotoxic effects. Specifically, the effect of chrysotile on cells is dose-dependent, resulting in increased levels of ROS and the development of oxidative stress, as well as a significant increase in the level of free-circulating mtDNA and decreased cell viability. Notably, surviving cells exhibit altered miRNAs expression [54]. Therefore, changes in the miRNA profile are a manifestation of the cellular response to toxic factors. This suggests a key role for miRNAs in stress-induced cellular senescence. In particular, mitomiRs, miRNAs localized in mitochondria and controlling their function, occupy a separate area of interest [55]. The study of mitomiRs holds significant promise

in the diagnosis and treatment of various diseases. The regulation of mitochondria by mitomiRs plays a crucial role in the pathophysiology of numerous diseases that result from mitochondrial dysfunction. Our previous research highlighted the significant role of mitochondrial miRNAs in the development of radon-induced and asbestos-induced lung cancer [56–58].

Some mitomiRs, known as SA-mitomiRs, have been reported to promote cellular senescence by affecting various pathways, including regulating p53/p21/p16/pRb signalling proteins as well as promoting SASP (Figure 2) [59,60]. p53/p21 and p16/pRb represent two complementary pathways involved in the regulation of cellular senescence. Both pathways are implicated in the initiation and duration of senescence. Although the p53/p21 pathway allows the initiation of cellular senescence, p16/pRb is responsible for its maintenance [61]. It has been observed that acute DNA damage under conditions of replicative senescence leads to temporary arrest of the cell cycle due to p53/p21 activation. In contrast, persistent DNA damage initiates p16/pRb expression, which ultimately promotes cellular senescence [62]. Regarding SASP and inflammation, the close relationship between SASP and senescence is well-documented [63]. Using bioinformatics analysis, Rippo et al. [64] showed that some mitomiRs (let-7b, miR-146a, -133b, -106a, -19b, -20a, -34a, -181a, and miR-221) are involved in cellular senescence via inflammation. Previously, it was proposed to update FRTA by unifying oxidation, age-related changes in mitochondrial function, and immune system function into the concept of "oxi-inflamm-aging" [65].

2.1. miR-146a

miR-146a is one of the most extensively investigated mitomiRs that are associated with the regulation of SASPs. It is particularly intriguing to note the relationship between miR-146a and cellular senescence, as well as inflammation. The activation of NF-κB initiates the transcription of mediators of SASP and miR-146a, which subsequently regulates TRAF6 and IRAK1 [66]. Through a negative feedback pathway, miR-146a acts as a negative regulator of inflammation by reducing the expression of proinflammatory cytokines [67–69]. However, the direct expression of miR-146a in senescent cells remains unclear. According to the study, there was an increase in the expression of miR-146a, as well as miR-181a and miR-34a, in the mitochondria of replicatively senescent human umbilical vein endothelial cells (sHUVECs) when compared to younger cells (yHUVECs) [70]. Similarly, miRNAs profiling in sHUVECs showed high activation of miR-146a, miR-9, miR-204 and miR-367 and their association with inflammation through toll-like receptor (TLR) signaling pathways [71]. Another investigation was conducted on sHUVECs, which demonstrated that miR-146a levels decreased as cells aged, and its overexpression led to fewer SA-β-gal-positive cells [72]. The targeting analysis showed that miR-146a targets NOX4 (NAPDH oxidase 4). Inhibition of NOX4 has been linked to reduced ROS generation, decreased oxidative stress and inflammation, and suppressed expression of VCAM-1 and ICAM-1 proteins [73].

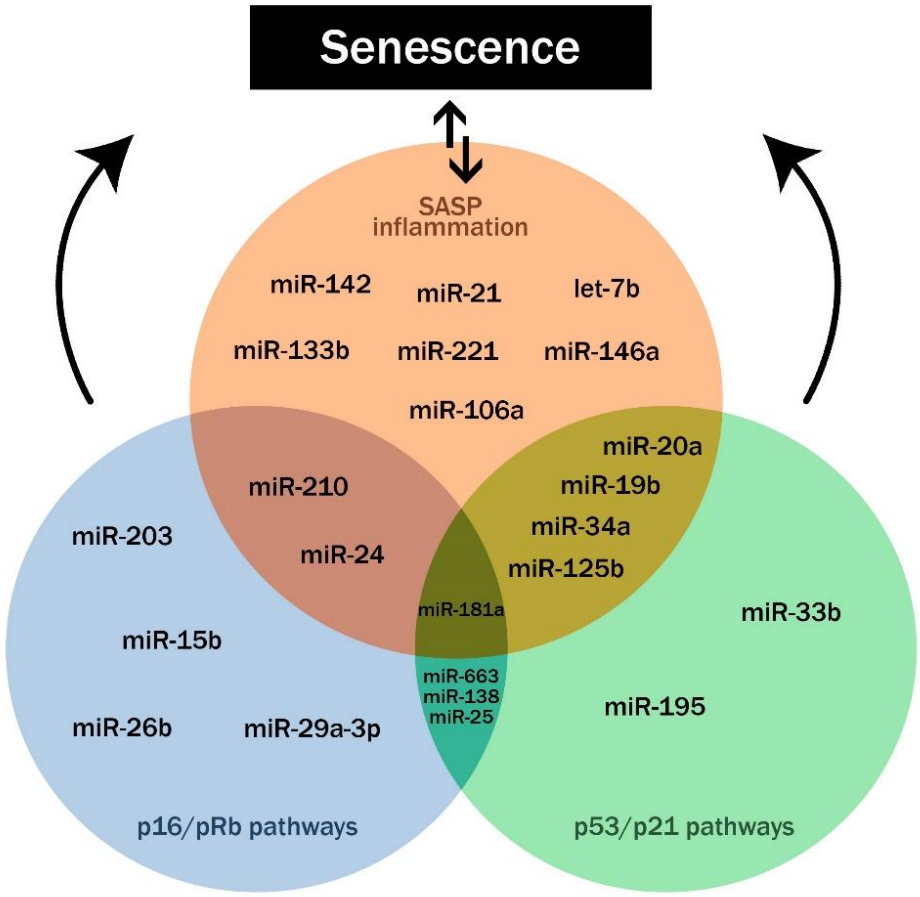

Figure 2. Venn diagram showing the mitomiRs involved in cellular senescence (SA-mitomiRs).

Schematic representation of the mitomiRs involved in cellular senescence through three major senescence mechanisms: the p53/p21 pathway (green circle), the p16/pRb pathway (blue circle), and SASP-induced inflammation (red circle). Common SA-mitomiRs for several mechanisms were presented at the intersection

2.2. miR-34a

The role of miR-34a as a significant inhibitory regulator of SIRT1 has been widely recognized and its involvement in the p53/p21 pathway is commonly referenced [60,74]. Sirtuins, more commonly known as SIRTs, play a important role in regulating mitochondrial function and overseeing the quality control of mitochondria through the process of mitophagy [75]. During cellular senescence, SIRT1 is identified as an autophagy substrate and undergoes cytoplasmic autophagosomal-lysosomal degradation via the major autophagy marker LC3 [76]. As SIRT1 levels decline with age, it may be linked to its ability to negatively regulate the expression of SASP factors [77]. Thus, we propose SIRT1 as an antagonist of senescence. These findings are

supported by a study on stress-induced senescence of human retinal endothelial cells (HuRECs), which showed increased expression of miR-34a, p21, and p16, and decreased levels of SIRT1. Accompanying these changes were impaired mitochondrial function and decreased levels of mitochondrial biogenesis factors such as PGC-1α, NRF1, and TFAM. However, the use of a miR-34a inhibitor prevented the observed mitochondrial dysfunction and stopped the overall increase in senescence markers [78].

2.3. miR-181a

Returning to the versatility of miRNAs in interacting with mRNAs, it is noteworthy that miR-34a is just one of several regulators of SIRT1. As reported by Munk et al. [60], miR-181a also targets SIRT1, allowing for the modulation of cellular senescence through p53 activation. Although miR-181a targeting SIRT1 may function as a senescence accelerator, some sources contradict this and suggest that it is the suppression of miR-181a-5p, along with the inhibition of miR-30a-3p and the overexpression of miR-30a-5p, that promotes cellular senescence [79]. his finding is inconsistent with the study by Huang et al. [80], which demonstrated that inhibition of miR-181a reduces stress-induced cellular senescence and oxidative stress.

2.4. miR-17-92 cluster: miR-19b and miR-20a

miR-17-92, one of the most well-studied clusters that includes miR-19b and miR-20a, has garnered significant interest since its discovery due to its oncogenic properties and link to aging [81]. A comprehensive study of multiple replicative senescence models demonstrated the suppression of miR-19b and miR-20a in six of them [82]. Apart from its role in tumorigenesis, the miR-17-92 cluster has also been shown to inhibit oncogene-induced cellular senescence by targeting p21 through miR-20a and miR-17, which slow down RAS-induced senescence in primary human fibroblasts BJ and WI38 [83]. Consequently, the miR-17-92 cluster highlights the interconnectedness of cellular senescence with the processes of carcinogenesis.

2.5. miR-29a-3p

miR-29 and miR-30 members of the family, which are regulated by pRb, exhibit heightened expression during both normal and premature senescence. These miRNAs have been implicated in the control of cellular senescence by suppressing the oncogene B-Myb [84]. Previous research has demonstrated that inhibition of B-Myb alone is sufficient to trigger senescence [85]. A comprehensive miRNA profiling analysis of human umbilical cord mesenchymal stem cells (UCMSCs) and cord blood mesenchymal stem cells (CBMSCs) identified 170 differentially expressed miRNAs, among which 83 miRNAs, including miR-29a-3p, were upregulated, while the remaining 87 miRNAs were downregulated [86].

2.6. miR-15b, miR-24 and miR-25

miR-15b, miR-24, and miR-25 have been found to act as inhibitors of cellular senescence, targeting MKK4 (mitogen-activated protein kinase kinase 4), which is significantly increased in senescent cells [87]. By inhibiting MKK4, these miRNAs suppress the p16/pRb pathway and delay the senescence of WI-38 fibroblasts. On the other hand, decreased expression of these

miRNAs promotes the senescent phenotype [88]. In addition, miR-25, in combination with miR-30d, negatively regulates the TP53 gene by reducing p53 protein levels and delaying the senescence process [89].

2.7. let-7 family: let-7b

let-7b is part of the largest and most conserved family of let-7 miRNAs. In their comprehensive study, Giuliani et al. [90] investigated the potential role of several senescence-associated mitomiRs, including let-7b, in the oxidative, inflammatory, and energy status of senescent cells, with a particular focus on let-7b, miR-1, and miR-146a-5p. By targeting mitochondrial proteins such as ATP6, ATP8, COX2, and ND5 [91], let-7b plays a critical role in mitochondrial function. Disruption of let-7b expression may lead to a loss of organelle integrity and function, initiating or exacerbating inflammatory responses and cellular senescence.

2.8. miR-221

The relationship between miR-221 and inflammation is fascinating. On one hand, it has been observed that miR-221 activates the NF-kB pathway in human endothelial cells [92]. On the other hand, there is a significant decrease in miR-221 expression in response to inflammatory stimuli [93]. The overexpression of miR-221-3p, miR-19b-3p, and miR-222-3p has been shown to increase intracellular ROS levels by targeting PGC-1α [94], which highlights the role of miR-221 in both inflammatory and antioxidant processes.

3. Differential Expression of MitomiRs in Radiation Responses

Comprehending the target genes involved in senescence and uncovering the pathways by which mitomiRs contribute to this process can shed light on the molecular basis of radiation-induced cellular senescence. By examining the differential expression of SA-mitomiRs after exposure to ionizing radiation, we can gain insights into the regulatory mechanisms underlying their interactions (Table 1). Targeting SA-mitomiRs may offer a new strategy for modulating radiation-induced cellular senescence and holds great potential for therapeutic intervention.

Table 1

The differential expression of SA-mitomiRs in response to exposure to ionizing radiation

SA-mitomiRs	Expression	Radiation	Effect	Ref.
miR-146a	↑	X-rays 1.7 Gy/min 4, 8, 12 and 24 h	Two induction peaks were observed after irradiation: one after 8 h and the other after 24 h	[95]
miR-34a	↑	^{137}Cs 5 Gy 5 days after irradiation	Increased expression promotes radiation-induced cellular senescence by targeting Myc. High levels of p16 and p21 and decreased levels of pRb in irradiated NSCLCs cells have been demonstrated	[96]

miR-181a	↑	X-rays 1.7 Gy/min 4, 8, 12 and 24 h	Induction of expression after exposure to ionizing radiation was only detected after 8 h	[95]
miR-19b	↓	^{137}Cs 5 Gy 1 h	Expression levels decreased exclusively during radiation-induced cellular senescence	[97]
miR-20a			Enhanced IR-induced cellular senescence in WI-38 fibroblasts and oxidative stress	
miR-29a-3p	↑	X-rays 7.5 Gy 14 days	A 4.17-fold increase in expression in senescent fibroblasts (HDFs), and overexpression of SASP factors, including IL1β, IL6, and IL8	[98]
miR-15b	↑	X-rays 1 Gy/min 24 h	Activation showed association with p53 and dose and time dependence of irradiation of HBECs cells. The maximum expression was reached 2 h after radiation exposure, after which the level gradually decreased	[99]
miR-24	↓	γ-radiation 5 Gy 24 h	The decline in miR-23a/27a/24-2 cluster activity induced by radiation in EA.hy926 and MCF10A cells is linked to the phosphorylation of AGO	[100]
miR-25	↑	^{137}Cs 5 Gy 1 h	Knockdown markedly attenuated radiation-induced cellular senescence	[97]
let-7b	↓	^{60}Co 150 and 180 cGy/min 1 h	Exposure to radiation results in decreased expression in HCT116 cells via a p53-dependent pathway, initiating the activation of ATM protein kinase	[101]
miR-221	↓	X-rays 0, 2, 4, 6 and 8 Gy 7 days	Both decreased expression levels and increased radiation dose induced G0/G1 cell cycle arrest	[102]
miR-142-3p	↑	X-rays 3 Gy 0, 4, 8, 12, and 24 h	Expression levels were upregulated in irradiated M059J and M059K glioblastoma cells	[103]
miR-142-5p				
miR-21	↑	^{60}Co 7 Gy 24 h	High expression in tissue samples of radiation-induced mouse thymus lymphoma tissue and targeting the Big-h3 tumor suppressor gene	[104]
miR-106a	↓	^{137}Cs 5 Gy 1 h	Decreased expression levels in radiation-induced and replicative cellular senescence	[97]

miR-206	↓	γ- radiation 20 Gy 12, 24 and 48 h	Reduced activity in response to exposure to ionizing radiation. However, the action of mimics resulted in the attenuation of radiation-induced neuroinflammation and reduced secretion of proinflammatory cytokines	[105]
miR-663	↓	X-rays 4 Gy 2 – 48 h	Suppression of activity in response to irradiation by binding TGFB1	[106]
miR-138	↑	2 Gy 1 h	Increased expression levels after irradiation of cancer cells initiate an immune response via the PD-L1/PD-1 axis	[107]
miR-210	↑	–	Overexpression of intestinal tissue samples from patients with radiation enteropathy	[108]

Note: NSCLCs – non-small-cell lung cancer cells; WI-38 cells – human embryonic lung diploid fibroblasts; HCT116 – human colorectal carcinoma cells; HDFs – human dermal fibroblasts; HBECs – human bronchial epithelial cells; EA.hy926 – human endothelial cell-line; MCF10A – mammary epithelial cell-line; M059J and M059K – human glioma cell lines; MCF-7 – human breast cancer cell line.

4. Bioinformatics Analysis of Enrichment of SA-mitomiRs Targets

Bioinformatic analysis of the target enrichment of miRNAs presented in this review using the MiRNA ENrichment TURned NETwork (MIENTURNET) [109] web tool revealed interactions between the PTPRD gene and 12 miRNAs (let-7b-5p, miR-106a-5p, -20a-5p, -133b, -142-5p, -195-5p, -19b-3p, -24-3p, -25-3p, -26b-5p, -29a-3p, and-34a-5p) (Figure 3).

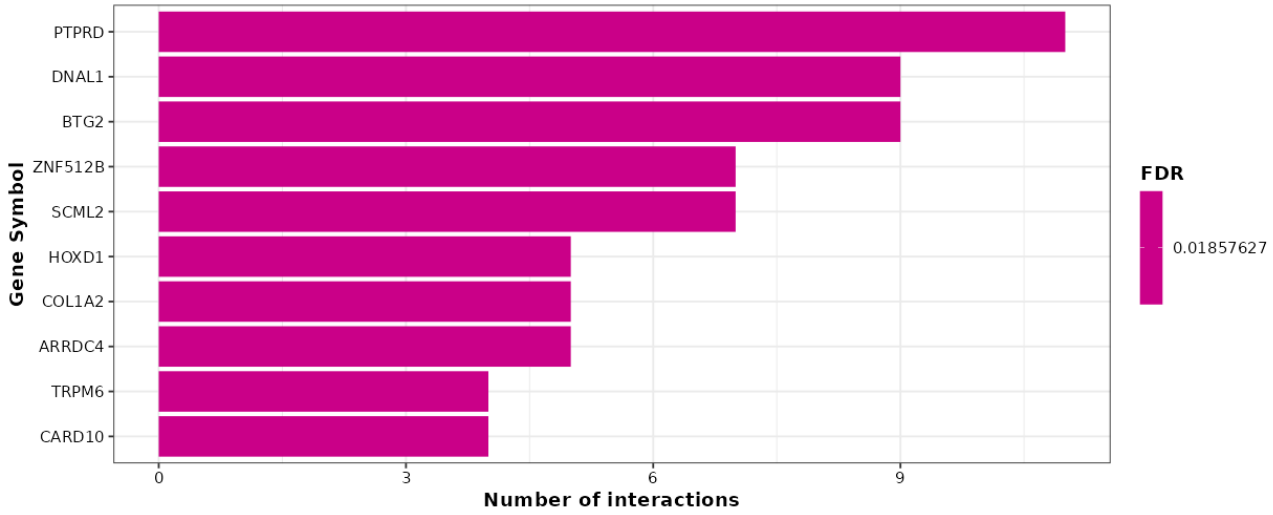

Figure 3. The bar graph of the results of the TargetScan-based enrichment analysis of mitoMirs targets

The color of the bars represents the adjusted p-values (FDR < 0.05)

PTPRD is a protein tyrosine phosphatase receptor type D encoding gene and is often inactivated as a tumor suppressor, along with Cdkn2a/p16 [110,111]. Overexpression of PTPRD has been shown to increase radiosensitivity by regulating cell death and promoting radiation-induced autophagy through direct targeting of STAT3 [112]. On the contrary, STAT3 activation cancels the effects of PTPRD overexpression [112], and loss of PTPRD leads to STAT3 hyperactivation [110].

STAT3 is a transcription factor that is involved in various cellular processes, such as carcinogenesis, inflammation, angiogenesis, and apoptosis. Additionally, the STAT3 pathway plays an important regulatory role in cellular senescence [113]. In a study by Pang et al. [114], STAT3 was defined as a biomarker of cellular senescence in liver fibrosis, with increased expression of STAT3 in senescent cells and a positive correlation with SASP factors (IL-6 and IL-1β). It has been reported that radiation-induced breast cancer senescent cells secrete SASP factors, which promote migration, invasion, and angiogenesis of neighboring cells through the activation of IL-6/STAT3 and PDGF-BB/PDGFR signaling pathways. In general, exposure to ionizing radiation activates STAT3 in cells and leads to increased IL-6 expression. However, STAT3 knockdown reduces radiation-induced STAT3 phosphorylation and pro-inflammatory interleukin production [115]. Furthermore, human coronary artery endothelial cells (HCECest2) subjected to radiation-induced cellular senescence demonstrated a bystander effect through their secretome in recipient cells, showing a similar inflammatory response and activation of the STAT3 pathway [116].

While STAT3's role as a transcription factor has been extensively studied over the past few decades, recent studies have revealed the existence of a mitochondrial pool of STAT3, known as mitoSTAT3, which functions as a positive regulator of the mitochondrial electron transport chain (ETC) [117]. Cells with inactivated STAT3 have been shown to have decreased activity of ETC complex I and II [118]. This pool of STAT3 has been found to be associated with ATP production and the modulation of mitochondrial ROS production. [119]. Furthermore, oxidative stress and cytokines have been found to deplete the mitoSTAT3 pool, and the chaperone protein cyclophilin D (CyPD) is required for its restoration. Restored STAT3 has been found to suppress stress-induced ROS formation in mitochondria [120].

Thus, the chain of interaction between mitomiRs, PTPRD, STAT3, and radiation-induced cellular senescence is quite intriguing, but the current state of research in this area is somewhat limited.

Conclusion

Given the numerous and intricate molecular mechanisms involved in radiation-induced cellular senescence, as well as the complex effects of ionizing radiation on humans, there is a need to search for new biomarkers to assess the extent of radiation damage. The search for the most suitable and highly sensitive biomarkers has led researchers to miRNAs. Considering the crucial role of mitochondria in cellular senescence, it is clear that it is worth studying mitochondrial miRNAs, or mitomiRs. To date, only a limited number of mitomiRs have been

thoroughly examined in relation to radiation-induced cellular senescence, and many remain unexplored.

In this review, we have focused on the most promising mitomiRs that play a role in radiation-induced cellular senescence. Nevertheless, additional research is required to comprehensively understand the function of mitomiRs in regulating ionizing radiation-induced cellular senescence.

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Author Contributions

Ibragimova M.A.: conceptualization, writing-original draft preparation, writing-review and editing and visualization.

Kussainova A.A.: conceptualization and writing-review and editing.

Aripova A.A.: writing-review and editing.

Bersimbaev R.I.: writing-review and editing.

Bulgakova O.V.: the corresponding author, conceptualization, writing-review and editing, supervision and funding acquisition.

All authors have made substantial contributions to the research, critically reviewed and approved the final version of the manuscript, and agreed to take responsibility for all aspects of the work, ensuring its accuracy and integrity.

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МитомиРлер: радиациядан туындаған жасушалық қартаюды реттеудегі митохондриялық микроРНҚ-ның рөлі

Аңдатпа. Иондаушы сәулеленудің адамға әсер ету мәселелері ғылымның әртүрлі салаларында көбірек назар аударады. Жақында радиацияның жасқа байланысты қаупі туралы көптеген мәліметтер жиналды, бұл иондаушы сәулелену мен жасушалық қартаю арасындағы байланысты анықтады. Бұл радиацияның жасушалық нысандарының бірі ретінде митохондрияларды іздеуге түрткі болды. Иондаушы сәулелену митохондриялардың бұзылуына және жасушаларға тән жасаралық фенотипінің пайда болуына әкеледі: ROS өнімдерінің жоғарылауы, SASP дамуы, эпигенетикалық профильдің өзгеруі және геномдық тұрақсыздық. Митохондриялық

дисфункция, көбінесе, жасушалық қартаюдың маңызды белгісі ретінде бағаланбайды, себебі, оның механизмдері өте кең және күрделі болып келеді. Атап айтқанда, митохондриялық гендердің экспрессиясын, демек, органеллалардың қызметі мен динамикасын реттейтін митохондриялық микроРНҚ (МитомиР) ерекше қызығушылық тудырады. МитомиР сәулелену кезінде пайда болатын маңызды емес бұзылуларға да ерекше сезімтал екенін ескере отырып, олардың экспрессиясында айтарлықтай өзгерістерге әкеледі, олар радиациялық әсердің перспективалы биомаркерлері ретінде қызмет ете алады. Бұл шолуда біз радиациядан туындаған жасушалық қартаюдағы мономерлердің негізгі рөлін растайтын дәлелдерді қарастырамыз және осы өзара әрекеттесудің негізгі молекулалық механизмдері туралы соңғы зерттеулерді біріктіреміз.

Түйін сөздер: жасушалық қартаю, иондаушы сәулелену, митохондриялар, митамиР, митохондриялық дисфункция, SASP.

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МитомиРы: Роль митохондриальных микроРНК в регуляции радиационно-индуцированного клеточного старения

Аннотация. Проблема воздействия ионизирующего излучения на человека привлекает все больше внимания в различных областях науки. В последнее время было собрано множество данных о возрастном риске радиационного облучения, что позволило выявить взаимосвязь между ионизирующем излучением и клеточным старением. Это послужило толчком к поиску клеточных мишеней радиации, в качестве одной из которых были определены митохондрии. Ионизирующее излучение приводит к нарушению работы митохондрий и проявлению характерного возрастного фенотипа клеток: повышенной продукции АФК, развитию SASP, изменению эпигенетического профиля и геномной нестабильности. Митохондриальная дисфункция часто недооценивается как важный признак клеточного старения, при этом механизмы, лежащие в ее основе, весьма обширны и запутанны. В частности, особый интерес представляют митохондриальные микроРНК (митомиРы), регулирующие экспрессию митохондриальных генов, и, следовательно, функцию и динамику самих органелл. Учитывая, что митомиРы особенно чувствительны даже к незначительным нарушениям, возникающим при облучении, что приводит к заметным изменениям в их экспрессии, они могут служить перспективными биомаркерами радиационного воздействия. В этом обзоре мы рассматриваем доказательства, подтверждающие ключевую роль митомиРов в радиационно-индуцированном клеточном старении, и объединяем самые последние знания об основных молекулярных механизмах, лежащих в основе этого взаимодействия.

Ключевые слова: клеточное старение, ионизирующее излучение, митохондрии, митомиРы, митохондриальная дисфункция, SASP.

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