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REVIEW ARTICLE

Role of miRNA-21 in radiation-induced heart disease

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Abstract

Radiation-induced heart disease (RIHD) is a potentially fatal clinical complication of chest radiotherapy (RT). RIHD is detrimental to the long-term health of post-RT survivors and limits the dose and intensity of RT required to effectively kill tumor cells. However, the cellular and molecular mechanisms underlying these effects remain largely unknown. MicroRNAs (miRNAs) are highly conserved, non-coding, single-stranded, small molecular RNAs that regulate gene expression and participate in cellular proliferation, apoptosis, differentiation, and disease development. MicroRNA-21 (miRNA-21) has become one of the most intensively studied miRNAs in the fields of cancer and cardiovascular disease in recent years. miRNA-21 plays an important role in RIHD progression. This article reviews the origin and function of miRNA-21 in the cardiovascular system and its role in RIHD pathogenesis. In addition, the potential role of miRNA-21 as a new target for predicting and treating RIHD is also discussed.

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Despite the increased overall survival rate in patients receiving radiation therapy, its side effects and sequelae have become major obstacles to the patients' quality of life in long-term survival, and radiation-induced heart disease (RIHD) is one of these vital detrimental factors [1]. When patients receive chest radiotherapy (RT), the heart is almost inevitably exposed to radiation, thus causing serious health complications that lead to RIHD [2]. In recent decades, RT techniques have been developed in a way that reduces such complications. However, these methods do not prevent exposure to cardiac radiation [3]. It may take decades for patients to manifest obvious RIHD symptoms after exposure to radiation [4]. Cardiomyopathy, pericarditis, coronary artery atherosclerosis, valvular disease, and conduction defects are common clinical presentations of RIHD [5]. The damage to the cardiovascular system caused by radiation is widely recognized and proved by numerous epidemiological, clinical, and preclinical studies [6, 7]. Nonetheless, owing to the complexity of the cardiovascular system and post-radiation effects, the mechanisms underlying RIHD still remain unknown.

MicroRNAs (miRNAs) are highly conserved non-coding single-stranded small molecular RNAs that mediate post-transcriptional gene silencing by binding to the 3' untranslated region (UTR) of target genes [8]. miRNAs are closely involved in regulating general cellular processes, such as cell proliferation and differentiation, which makes them highly associated with disease onset [9]. A recent study showed differential expression levels of miRNAs in different pathological conditions, including RIHD [10].

miRNA-21 is a widely studied miRNA that is expressed in the majority of human cells, including macrophages, monocytes, myocardial cells, and dendritic cells [11]. The studies of miRNA-21 are mainly involved with its epigenetics function in oncology and cardiology. The expression of miRNA-21 is maintained through transcription and post-transcriptional regulation [12]. Non-transcriptional upregulation of miRNA-21 has also been proposed as a supplement [13, 14]. Radiation leads to increased miRNA-21 expression levels. Kwon *et al.* [15] found increased miRNA-21 levels in irradiated sites in mice. Similar findings in the serum of patients with breast cancer who underwent RT were reported by Halimi *et al* [16], suggesting that serum miRNA-21 may be utilized as a biomarker to identify patients exposed to ionizing radiation. Additionally, fibrosis may result from the persistent overexpression of miRNA-21 [17]. According to Lin *et al* [18], miRNA-21 upregulates SIRT1 and is involved

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with the process of fibrosis via TGF- β1 pathway.

In the pathogenesis of RIHD, the role of miRNA-21 remains unknown. Previous scientific studies have reported the involvement of miRNA-21 in the pathology of cardiovascular disease and cancer; however, few have focused on the effects of irradiation on the cardiac system and the mechanisms involving miRNA-21 in such processes. Herein, we summarize the basic biology and mechanisms underlying miRNA-21 involvement in RIHD and the cardiovascular system and discuss its potential as a biomarker and future therapeutic target.

Biogenesis of miRNA-21

miRNA-21 is one of the first miRNAs to be discovered, and the human miRNA-21 gene is located in the intergenic region on the 3' UTR end of transmembrane protein 49 (TMEM 49), which is also known as protein with human vacuolar membrane 1 (VMP1), on chromosome 17q23.2 [19]. The miRNA-21 gene has a total of 3433 nucleotides, and there are two transcription sites within the locus: one major transcription site approximately 3.5 kb in size and one minor transcription site approximately 4.3 kb in size. In the nucleus, these transcription sites are initiated by RNA Polymerase II (RNAP II) to synthesize pri-miRNA-21 [20]. After transcription, pri-miRNA-21 is processed by Drosha endonuclease (an RNase III) and dgcr8 (a dsRNA-binding protein) into pre-miRNA-21 72 bases in size (precursor miRNA-21), which is transported from the nucleus to the cytoplasm by exportin 5 [21]. The pre-miRNA-21 structure's last loop is cut by cytoplasmic Dicer (an RNase III endonuclease), and the nucleotide sequence is processed into a mature single-stranded nucleotide sequence, miRNA-21, with a length of 22 nucleotides. Mature miRNA-21 is associated with the RNA-induced silencing complex (RISC), a cytoplasmic protein complex [22]. The domain at the 5' end of miRNAs in this miRNA-RISC complex targets the 3' UTR of the target mRNAs. RISC promotes protein downregulation by inhibiting or degrading mRNA after binding to their UTR in a complementary base-pairing manner [23].

In combination with RNAP II, the miRNA-21 gene in the nucleus is transcribed into pri-miRNA, which is the most primitive form of miRNA-21. Pri-miRNA-21 is further processed by Drosha (an RNase III endonuclease) and DGCR8 (a dsRNA-binding protein) to become pre-miRNA-21, which is the miRNA precursor, approximately 70–90 bases in size. This precursor is transferred from the nucleus to the cytoplasm through exportin 5 (Exportin 5). The circular structure of pre-miRNA-21 is removed after digestion with the Dicer (an RNAse III endonuclease) in the cytoplasm to form mature miRNA (miRNA/miRNA duplex) in a double-stranded structure. After processing by Dicer, transactivation response RNA binding protein (TRBP), and protein kinase RNA activator (PACT), these miRNA duplexes unwind into single strands, and some of these miRNAs may become circulating miRNAs after secretion. However, miRNAs that remain in the cell participate in the formation of the RISC, which can combine with mRNA or target genes to play a regulatory role in translation (Fig.1).

miRNA-21 in the cardiovascular system

miRNA-21 primarily contributes to cardiovascular disease by controlling the expression of its downstream target genes. Target genes that have been extensively studied include programmed cell death protein 4 (PDCD4) [24], sprouty1 (SPRY1), sprouty2 [25] and phosphatase and tensin homolog deleted from chromosome 10 (PTEN) [26]. In addition, some target genes have also been considered as specific binding sites of miRNA-21 in recent decades, including peroxisome proliferator-activated receptor alpha (PPAR-α) [27], factor related apoptosis ligand [28], a-kinase anchoring protein 8 (Akap8), BRCA1 associated RING domain 1 (Bard1) [29], Jagged 1 [30], and hypoxia inducible factor-1 alpha (HIF-1α) [31].

In the cardiovascular environment, the role of miRNA-21 in the PTEN pathway is of primary concern, and most studies have focused on apoptosis of cardiomyocytes in this pathway. miRNA-21, through the inhibition of the PTEN pathway, protects the heart from apoptosis [32]. One study demonstrated that miRNA-21 is involved in regulating pathological symptoms and cardiomyocyte apoptosis in hypertensive rats through the PTEN/PI3K/Akt/mTOR signaling pathway [33]. Furthermore, miRNA-21 is a central regulator of cardiac fibrosis [34]. Previous *in vivo* and *in vitro* experiments have focused on miRNA-21 inhibition to regulate the PTEN pathway, which shows a protective effect of miRNA-21 against pathological injury and aging. Bei Y *et al*. showed that inhibiting miRNA-21 had the same protective effect against d-galactose-induced cardiac alterations and doxorubicin-induced cardiomyocyte senescence by targeting PTEN [35]. In an *in vitro* model of myocardial I/R injury, Huang J *et al*. demonstrated that miRNA-21 mediates the protective effects of kaempferol against hypoxia/reoxygenation-induced H9c2 cell injury by promoting the Notch/PTEN/Akt signaling pathway [36].

Similarly, miRNA-21 inhibits the pro-apoptotic effect of PDCD4, showing the protective effects of miRNA-21 in heart cardiomyopathy. Xiao J *et al*. indicated that exosomal miRNA-21 prevents cardiomyocyte apoptosis by targeting PDCD4 [37]. Overexpression of miRNA-21 inhibits PDCD4, suppresses activator protein-1 (AP-1) inhibition by PDCD4, and leads to the upregulation of AP-1. AP-1, being a transcription factor, is able to directly promote miRNA-21 expression, thus forming a

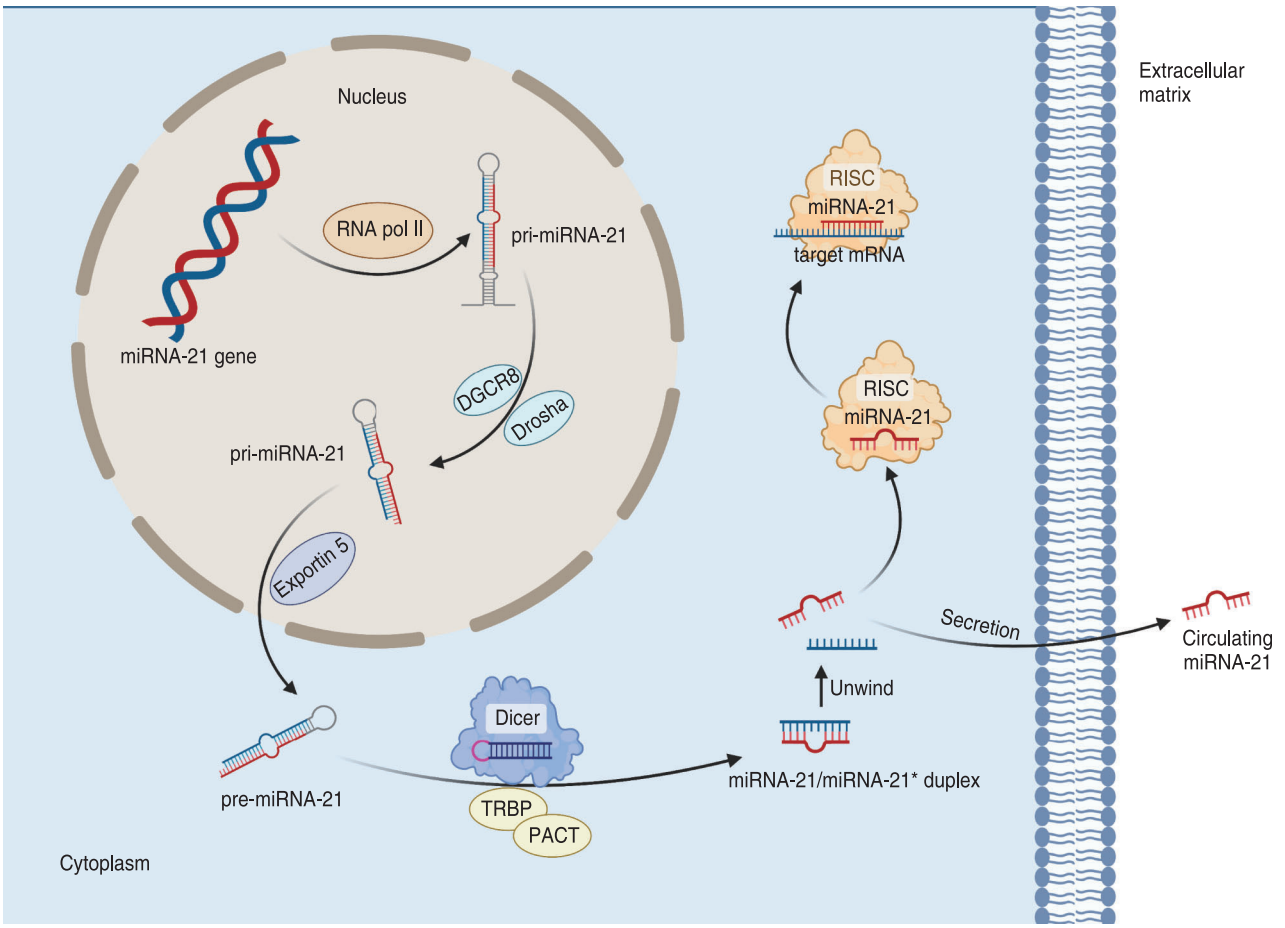

Fig. 1 miRNA-21 biogenesis of miRNA-21.

positive feedback loop in this pathway [38] Recent scientific reports on mice also confirmed that the suppression of miRNA-21 prevents hypertrophic stimulation-induced cardiac remodeling by regulating PDCD4, AP-1, and TGF-β1 signaling pathway [39].

However, in the Smad7/Smad2/3 pathway, miRNA-21 has an inhibitory effect on Smad7, thereby increasing collagen deposition, inducing the TGF-β1 pathway, and leading to α-smooth muscle actin and filamentous actin polymerization, which in turn promotes the development of myocardial fibrosis [40]. Similar pro-fibrotic effects of miRNA-21 have been reported in the spry/ERK/mTOR pathway [41]. Li X *et al.* found that miRNA-21 knockout DM mice had reduced cardiac hypertrophy and cardiac dysfunction compared to wild-type diabetes mellitus (DM) mice and concluded that miRNA-21 overexpression reduced autophagy by inhibiting the spry1/ERK/mTOR pathway and aggravated fibrosis in miRNA-21 knockout DM mice [42].

Some relatively novel miRNA-21 specific binding sites have also been reported in recent research. Peroxisome proliferators-activated receptors (PPARs) are ligand activated receptors in the nuclear hormone receptor family, of which PPARα isoforms are highly expressed in the heart and are one of the key receptors involved in regulating fatty acid metabolism. Chuppa S *et al.* used next-generation mRNA sequencing to identify novel molecular mediators in a 5/6 nephrectomy rat model of chronic kidney disease, and the results revealed that miRNA-21-5p suppression altered gene expression in PPARα regulated pathways in the left ventricle, which identified PPARα as a potential therapeutic target for CKD-related cardiac dysfunction [27].

The rat cardiomyocytes study by Shen H *et al.* identified that miRNA-21 significantly enhanced hypoxia/reoxygenation-induced apoptosis, indicating that miRNA-21 is directly targeted to the 3' UTR of Akap8 and Bard1 mRNA. miRNA-21 exerts protective effects against H/R-induced apoptosis and reactive oxygen species (ROS) production in cardiomyocytes via this mechanism [29]. Zhou XL *et al.* found that miRNA-21 targeted the 3' UTR end of Jagged1 and promoted the transformation of rat cardiac fibroblasts to myofibroblasts. TGF-β1 also induced miRNA-21 expression and inhibited Jagged1

expression. While by targeting Jagged1, miRNA-21 in turn influenced TGF-β1 on the transformation of rat cardiac fibroblasts into myofibroblasts and resulted in cardiac fibrosis [43]. Cao, W *et al.* concluded that tumor suppressor cell adhesion molecule 1 (CADM1) is regulated by miRNA-21, which promotes cardiac fibrotic remodeling and fibroblast proliferation by targeting CADM1 [44].

miRNA-21 and RIHD

Radiation damage to the heart mainly manifests as the production of free radicals, leading to the development of inflammatory processes [45]. Radiation exposure also leads to significant changes in the expression of many proteins, including prostaglandins, prostacyclins, thromboxanes and leukotriene [46]. These inflammatory factors contribute widely to vasodilation, vasoconstriction, increased microvascular permeability, and thrombosis in patients with RIHD. Irradiation can damage the capillary endothelium, resulting in decreased myocardial perfusion and ischemia [47].

About 150–200 miRNAs are expressed in cardiac myocytes [23], many of which are dynamically regulated in response to cardiovascular toxicity following irradiation. miRNAs participate in the pathological processes of radiation-induced myocardial fibrosis, including DNA damage, oxidative stress, inflammation, endothelial dysfunction, hypertrophy, and fibrosis [48].

Kura B *et al.* indicated that miRNA-21 is widely involved in the pathological processes of RIHD, including oxidative stress, fibrosis, hypertrophy, ischemia, preconditioning, and inflammation [49]. After chest irradiation, miRNA-21 was upregulated in cardiomyocytes, where it acted as a regulator of growth factors secretion in cardiac fibroblasts, their survival, and the ERK/MAPK pathway, eventually leading to myocardial hypertrophy and myocardial fibrosis [50]. PDCD4 is also considered a potential target of miRNA-21, along with other cardiac protective mediators related to miRNA-21, such as AP-1, heat shock protein-70, endothelial nitric oxide synthase, and heat shock transcription factor-1 [51].

Prognosis

Ionizing radiation stimulates miRNA-21 expression in various mammalian cell types, including cardiomyocytes, fibroblasts and macrophages [45]. This significant upregulation in cardiomyocytes after irradiation indicates that miRNA-21 has the potential to become a predictive tool for RIHD.

After administering a single dose of 25 Gy radiation to the mediastinum, Kura B. *et al.* [48] discovered that myocardial miRNA-1 was downregulated, whereas miRNA-21 was upregulated after 6 weeks. These findings were supported by further research published in 2019, which showed that miRNA-21 was upregulated in the left ventricle of rats following mediastinal irradiation with 10 Gy [52].

According to a study by Slezak J *et al.*, the expression of microRNA-21 in rat hearts increased approximately 10-fold after 6 weeks of 25 Gy mediastinal irradiation, indicating a compensatory/protective impact in the myocardium 6 weeks after radiation [45]. Similar findings were reported by Viczenczova C *et al.* [50], where an increase in miRNA-21 expression was closely associated with an increase in Cx43 expression in the irradiated rat heart. In addition, under diverse oxidative stress situations, the expression of miRNA-21 increased in human fibroblasts [53].

Kwon OS *et al.* discovered that radiation raised the expression of miRNA-21 in a mouse model [15]. Similar findings were reported in the serum of irradiated patients by Halimi M *et al.* [16], indicating that human miRNA-21 is a possible biomarker for radiation exposure. Experimental data from rats showed that 8 Gy of total body irradiation led to cardiac fibrosis, which was related to miRNA-21 upregulation. The hearts of rats in the control group showed reduced collagen and fibrosis [54].

Many studies reported the upregulation of miRNA-21 expression after cardiac irradiation, where the key pathway regulated by miRNA-21 is tightly related to the cardiac pathogenesis, such as in cardiac fibrosis. However, because miRNA-21 is widely present in human cells and miRNA expression is regulated by a complicated mechanism, consistent results from studies with various samples from different individuals are still missing. Other studies were not limited to using miRNA-21 as a single biomarker but attempted to find a combination of miRNAs that can be used as specific biomarkers for cardiovascular disease [55, 56]. To obtain consistent outcomes, several significant clinical investigations are needed, and the potential of miRNA-21 as a biomarker for the early detection of heart disease and RIHD remains controversial.

Mechanism

Radiation exposure affects cardiac capillary endothelial cells, causing proliferation, damage, swelling, and degeneration of endothelial cells and a significant decrease in the number of capillaries [57]. Radiation-induced endothelial cell injury is the primary cause of myocardial injury following radiation exposure [58]. This kind of reduction causes chronic hypoxia that is also a cause of fibrosis via stabilizing hypoxia-inducible factor 1α (HIF-1α) [59], which was reported as one of the targets of miRNA-21 [31]. HIF-1α can directly or indirectly facilitate fibrosis by stimulating various pro-fibrotic mediators in the cardiovascular system, such as TGF-β, endothelin-1, connective tissue growth factor, as well

as vascular endothelial growth factor (VEGF) [60]. In a guinea pig experiment, the expression of miRNA-21 was confirmed to be positively correlated with VEGF and HIF-1 [61]. Similar conclusions have been reached in patients with neoplasms [62]. According to Mace, T.A. *et al.*, hypoxia in pancreatic cancer cells induces miRNA-21 via the overexpression of HIF-1α [63], which showed that miRNA-21 has an anti-apoptotic effect in HIF-induced hypoxia environment. *In vitro*, RT-PCR results showed that miRNA-21 can target PTEN, activate the AKT and ERK1/2 signal transduction pathways, and increase the expression of HIF-1 and VEGF. HIF- 1α is the primary downstream target of miRNA-21, which controls angiogenesis [64].

Monocyte migration to the intima is also a result of radiation damage. Radiation damage with a dose ≥ 2 Gy in endothelial cells can stimulate the expression of inflammatory factors, such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin. These factors increase the invasiveness of monocytes in tissues [65]. Monocytes gradually transform into activated macrophages and secrete a large amount of TGF-β during the process of recruitment to the intima, inducing smooth muscle cells to differentiate into myofibroblasts and produce a large amount of type IV collagen [66]. The profibrotic effect of miRNA-21 in cardiac fibroblasts is inextricably linked to TGF-β, which induces the process of epithelial-mesenchymal transition [67, 68]. Cardiovascular fibroblasts treated with miRNA-21 mimics can produce and secrete a large amount of TGF-β1, and in a similar way, cardiac fibroblasts transfected with TGF-β1 enhance miRNA-21 expression [69]. Additionally, by suppressing Smad7 expression, miRNA-21 lessens the Smad7 pathway's inhibitory influence on TGF-β1, which greatly contributes to the development of cardiac fibrosis [40].

As another major pathological mechanism of RIHD, irradiation induces the superoxide overproduction and cardiomyocyte apoptosis of intracellular ROS in cardiomyocytes [70]. Pro-oxidant enzymes, particularly NADPH oxidases, are heavily controlled by a variety of growth factors and cytokines, including TGF-β, and irradiation can also result in an aberrant increase in these enzymes [71]. ROS can encourage the initiation and continuation of the pro-fibrotic process through TGF-β1. ROS acts as an intracellular second messenger that can also regulate the nuclear factor-κB (NF-κB) pathway to mediate epigenetic regulation of fibroblasts and induce fibroblast to myofibroblast differentiation [72, 73]. By specifically targeting the PDCD4 gene, miRNA-21 shields cardiomyocytes from myocardial infarction and injury caused by ROS [74, 75]. In cardiac myocytes overexpressed with ROS, miRNA-21 can directly target PDCD4, which also proves that NF-κB can promote cell death by regulating the excessive production of miRNA-21 [76].

Bax, a member of the Bcl-2 family, is also a target of miRNA-21 via various apoptotic pathways [77]. Exposure to radiation increases Bax expression and activation, which causes it to move and insert into the outer mitochondrial membrane [78, 79]. This regulation accelerates the opening of mitochondrial voltage-dependent anion channels, thereby increasing mitochondrial membrane permeability, and finally, swelling of the mitochondrial membrane leads to apoptosis [80]. Overexpression of miRNA-21 downregulates PTEN, which activates the PI3K/Akt pathway and subsequently inhibits the pro-apoptotic function [81], promoting the survival and proliferation of myocardial cells through anti-apoptotic effects.

By activating the ERK/MAP kinase pathway, radiation also inhibits PPAR-α to lower energy production from fatty acids [82]. When 8 or 16 Gy of single dose cardiac radiation were administered to C57BL/6 mice, the activated phospho-ERK phosphorylated PPAR-α, which resulted in a protein conformational change and subsequent inactivation of PPAR-α complex. This process leads to abnormal myocardial lipid metabolism and mitochondrial function damage that triggers the process of cell apoptosis [83]. Inhibiting the expression of miRNA-21-5p could upregulate the gene expression in the PPAR-α pathway [27], and PPAR-α downregulation could weaken the impact of miRNA-21-5p gene knockdown, including cell growth and infiltration[84].

miRNA-21 plays a dual role in RIHD. miRNA-21 inhibits the PPAR-α pathway to achieve an anti-apoptotic effect, reflecting the protective role of miRNA-21 against radiation, which can promote the inhibition of ERK/MARK pathway and PPAR-α, leading to cell apoptosis through the mitochondrial pathway. miRNA-21 also affects the Bcl-2/Bax/caspase-3 signaling pathway by targeting PTEN and regulating apoptosis. Similarly, miRNA-21 inhibits the expression of PDCD4 to protect myocardial cells from apoptosis. ROS produced during RT mediates the NF-κB pathway to directly promote the overexpression of miRNA-21, which antagonizes ROS-induced apoptosis. In addition, PDCD4 inhibits the upregulation of AP-1, and AP-1 can, in turn, directly promote the expression of miRNA-21, forming a positive feedback loop between miRNA-21 and AP-1. In contrast, miRNA-21 enables promotion of myocardial fibrosis mainly by regulating the Smad7/Smad2/3 pathway. Radiation can stimulate various types of cardiac cells to produce inflammatory factors, such as TGF-β1, VCAM, ICAM and E-selection, which enhance the expression of the smad2/3 pathway and further promote myocardial fibrosis. RIHD, peroxisome proliferator-activated receptor alpha(PPAR-α), Extracellular signal-regulated kinase (ERK) mitogen-activated protein

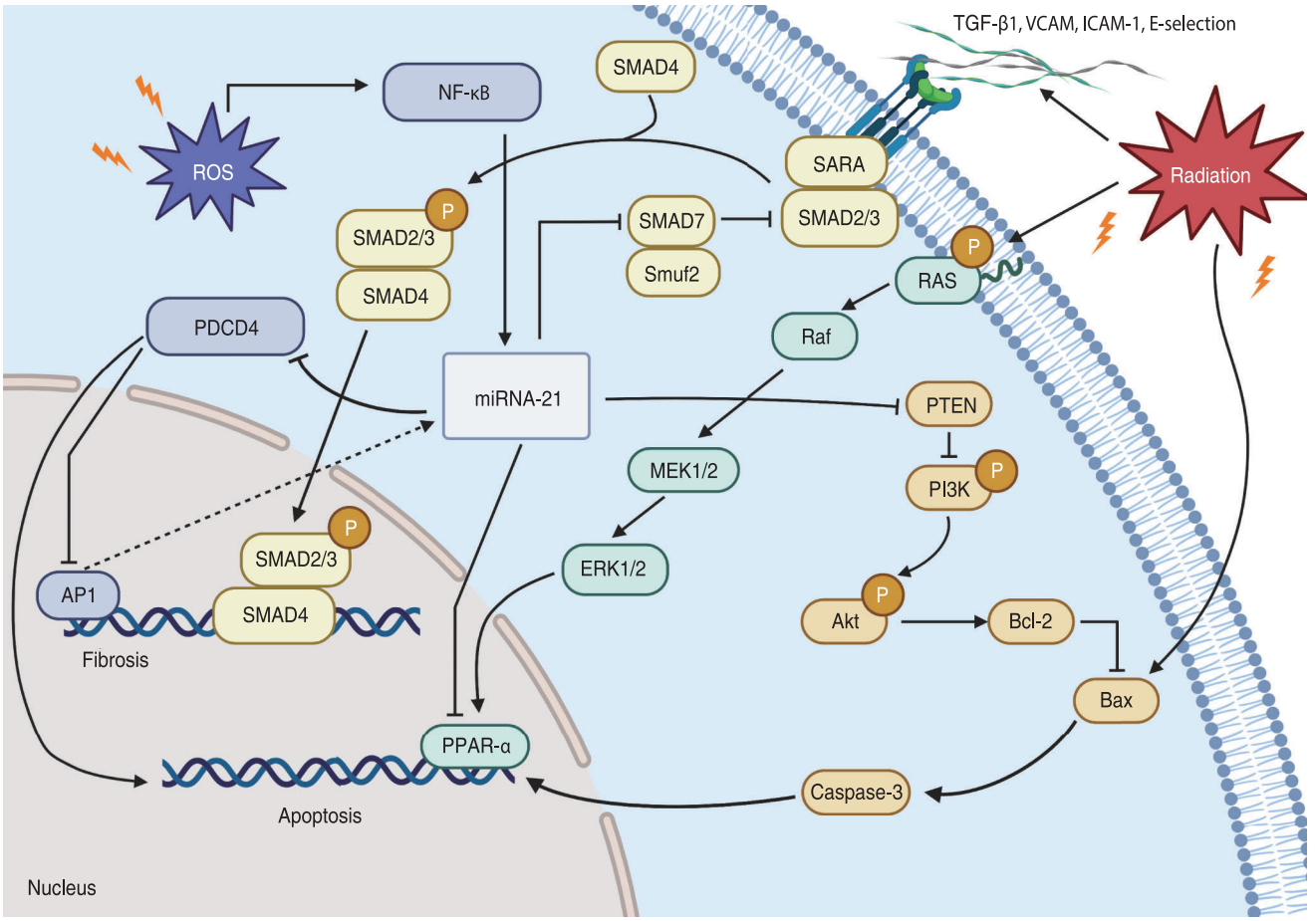

Fig. 2 The molecular mechanisms of miRNA-21 in RIHD.

kinase (MARK), B-cell lymphoma 2 (Bcl-2), bcl-2-like protein 4 (Bax), Phosphatase and tensin homolog deleted from chromosome 10 (PTEN), Programmed Cell Death 4 (PDCD4), Reactive oxygen species (ROS), Nuclear factor kappa-B (NF-κB), Activator protein-1 (AP-1), SMAD Family Member2/3/4/7 (Smad2/3/4/7), Transforming growth factor-β1 (TGF-β1)), Vascular cell adhesion molecule (VCAM), and Intercellular cell adhesion molecule (ICAM). This Figure was created using Biorender.com (Fig.2).

Therapy

In recent years, miRNA-based drugs have become popular owing to their high biological stability and advantage of being potential biomarkers [85]. There are currently three types of miRNA-based drugs [86]: AntagomiRs, which bind to the target miRNAs to specifically inhibit their function, resulting in reduced activation of RISC and upregulation of genes and production of proteins [87, 88]; synthetic miRNA mimics is an approach for gene silencing [89]. This kind of generated artificial double-stranded miRNA-like RNA fragments can target mRNA and activate RISC, which leads to their suppression and the reduction of overexpressed miRNAs in disease conditions [90]. Another lesser known approach involves miRNA sponges, masks, and erasers [91]. miRNA sponges are competitive inhibitors of miRNA target genes, which can engulf miRNAs-of-interest inside the cell, similar to water absorption by a sponge, leading to blocking of the activity of miRNAs [92, 93]. Erasers are oligonucleotides complementary to specific miRNAs that inhibit their function [94]. miRNA-masks are antisense chains that are completely complementary to the binding sites of miRNA and target mRNA; hence, they can form a complex with the target mRNA and act as a target protector to conceal the binding sites, thus interfering with the binding of the corresponding miRNA and target mRNA [95]. Lu YJ *et al.* proposed multi-target anti-miRNA antisense nucleotide inhibitors [96].

miRNA-21 is considered a potential therapeutic target for cardiomyopathy. One study demonstrated that miRNA-21 is a mediator involved in the pathogenesis of cardiac fibrosis, and using locked nucleic acid (LNA) anti-miRNA-21 can cause miRNA-21 inhibition, leading

to a reduction in collagen expression and alleviation of cardiac fibrosis [67]. Certain drug studies have focused on inducing or inhibiting the expression of miRNA-21 at the transcriptional level. By using melatonin (MET) entrapped poly nanoparticles (MET/PLGANPS), Wang S *et al*. proved the therapeutic effect of MET/PLgANPS in RT, and MET/PLGANPS may inhibit the miRNA-21/TGF- β1/Smad3 pathway to reduce the injury after radiation [97]. Kura B *et al*. showed that Enbrel and tadalafil changed miRNA expression values of irradiated rats to those of non-irradiated controls, thus contributing to the alleviation of radiation-induced toxicity [48]. Another study indicated that molecular hydrogen is a potential therapeutic agent that decreases myocardial miRNA-21 levels after irradiation by affecting the intracellular ROS levels [52]. Promotors such as AP-1, STAT3, Ras, ERK1/2, and EGFR can effectively induce miRNA-21 expression [98–101]. In contrast, some transcriptional suppressors, such as NFI, C/EBP, Gfi1, and estrogen receptors, have also been reported to repress miRNA-21 transcription [102, 103].

However, the main drawback of using miRNAs for diagnosis or therapy is that they target and affect the expression of multiple genes. Therefore, their targeting may also have an impact on other pathways in the organism [104]. MiRNA-21 is not necessarily a cell type-specific miRNA and hence is problematic for targeted therapy, and application of the miRNA-21 expression pattern in cardiomyopathies for repression or restoration is challenging [105].

Conclusion and perspective

The etiology and mechanism of occurrence after RIHD are not fully defined. Besides cardiomyocytes, some other cardiac cells also participate in the occurrence and development of this type of cardiomyopathy, such as endothelial cells, smooth muscle cells, fibroblasts, and immune cells [106]. Similarly, noncardiomyocytes play important roles in cardiomyocyte apoptosis, cardiac fibroblast activation, and immune cell infiltration [107]. Expression profiles of miRNAs may differ in cells of diverse origins [108, 109]. miRNA-21 has different expression characteristics and functions in various cardiac cell s [110]. Though miRNA-21 plays an important role in radiation-induced cardiac injury, the regulatory details of miRNA-21 in the processes of biogenesis, secretion, and degradation remain unclear. The use of miRNA-21 as an independent biomarker for diagnosis or prognosis persists to be challenging. Further research is required to determine the pathogenesis and mechanism of action of miRNA-21 in RIHD. With miRNA-21, there are still many other kinds of miRNAs that have been reported in the field of RIHD, such as miRNA-1 and -15b [52], miRNA-22, miRNA-24, miRNA-29, miRNA-133 [111], miRNA-208, miRNA-29, miRNA-199b, miRNA-221, miRNA-222, and the miRNA-15 family [49]. miRNA-15b is a regulator of cardiac hypertrophy and fibrosis as it inhibits the TGF-β Signal pathway after irradiation [112]. The miRNA-29 family targets mRNAs of various types of elastin, fibrin, and collagen (including type I and type III collagen) involved in fibrosis, which is a key pathological change related to RIHD in irradiated rats [45]. Cardiac specific miRNA-208 has been proved to be crucial to cardiac hypertrophy, fibrosis, and the expression of β-myosin heavy chain [113].

In conclusion, miRNA-21 is a critical miRNA that is involved in RIHD. Specific miRNA-21 studies have revealed the cellular and molecular mechanisms of RIHD, and its potential therapeutic role is still promising based on further animal experiments and clinical trials.

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Conflicts of interest

The authors indicated no potential conflicts.

Author contributions

Zhijie Fan prepared the manuscript draft and created the figures, Motuma Yigezu Daba prepared the manuscript draft, Lingyan Xiao polished the manuscript, and Xianglin Yuan revised the manuscript. All the authors have read and approved the final manuscript.

Data availability statement

Not applicable.

Ethical approval

Not applicable.

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