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REVIEW ARTICLE

MicroRNA: a novel implication for damage and protection against ionizing radiation

Yonglin Chen[1,2] · Jian Cui[1,2] · Yaqi Gong[1,2] · Shuang Wei[1,2] · Yuanyun Wei[1,2] · Lan Yi[1,2]

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Abstract

Ionizing radiation (IR) is a form of high energy. It poses a serious threat to organisms, but radiotherapy is a key therapeutic strategy for various cancers. It is significant to reduce radiation injury but maximize the effect of radiotherapy. MicroRNAs (miRNAs) are posttranscriptionally regulatory factors involved in cellular radioresponse. In this review, we show how miRNAs regulate important genes on cellular response to IR-induced damage and how miRNAs participate in IR-induced carcinogenesis. Additionally, we summarize the experimental and clinical evidence for miRNA involvement in radiotherapy and discuss their potential for improvement of radiotherapy. Finally, we highlight the role that miRNAs play in accident exposure to IR or radiotherapy as predictive biomarker. miRNA therapeutics have shown great perspective in radiobiology; miRNA may become a novel strategy for damage and protection against IR.

Keywords Ionizing radiation · MicroRNA · Cellular response · Cancer · Radiotherapy · Biomarker

Abbreviations

ATM	ataxia-telangiectasia mutated
AKT	RAC-alpha serine/threonine-protein kinase
A549	a type of non-small cell lung cancer cell
BAX	Bcl-2-like protein 4
BCL-2	B cell lymphoma 2
CDC25A	cell division cycle 25A
CDK	cyclin-dependent kinase
CHK	checkpoint kinase
c-Myc	Myc proto-oncogene protein
DSB	DNA strand break
EGFR	epidermal growth factor receptor
EMT	epithelial-to-mesenchymal transition
HIF-1α	hypoxia-inducible factor 1-α
HR	homologous recombination
IR	ionizing radiation
miRNA	MicroRNA
mTOR	mechanistic target of rapamycin kinase
NHEJ	non-homologous end joining
NSCLC	non-small cell lung cancer
PTEN	phosphatase and tensin homolog
PI3K	phosphoinositide 3-kinase
P21	cyclin-dependent kinase inhibitor 1A
P53	cellular tumor antigen p53
RAD51	DNA repair protein RAD51 homolog 1
ROS	reactive oxygen species
ZEB1	zinc finger E-box-binding homeobox 1

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✉ Lan Yi
yilanoky@126.com

[1] Hengyang Medical College, Institute of Cytology and Genetics, The Hengyang Key Laboratory of Cellular Stress Biology, University of South China, Hengyang 421001, Hunan Province, People's Republic of China

[2] Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study, Hengyang 421001, Hunan Province, People's Republic of China

Introduction

Ionizing radiation (IR) is a form of high energy consisting of alpha and beta particles as well as electromagnetic energy radiation including gamma and X rays. It acts through high energy physics via damaging factors by producing intermediate ions and free radicals that damage the chemical structure of DNA with DNA strand breaks (DSBs) as the most lethal injury (Carter et al. 2019; Smith et al. 2017). IR-induced DSBs trigger DNA damage repair mechanisms among which non-homologous end joining (NHEJ) and homologous

recombination (HR) are the two main pathways (Mueck et al. 2017). When DNA damages caused by IR are over the cellular ability to repair, improper DNA repair will lead to cell death. (Shimizu et al. 2015). At the organism level, high-dose radiation causes acute radiation sickness and severe diseases such as leukemia, thyroid, breast, and skin cancers, and cataracts (Douple et al. 2011; Hamada and Sato 2016; Mettler Jr. et al. 2007). Low-dose radiation does not have severe effects, but long-term exposure to low-dose radiation leads to an increased risk of leukemia, lymphoma, and abnormalities in the central nervous system (Spycher et al. 2015). In the clinic, radiotherapy has been widely used for medical diagnostics and cancer-related therapy, especially for the treatment of localized solid cancers (Schaue and McBride 2015). However, the effect of radiotherapy is generally limited by radioresistant cancer cells (Peters et al. 1982). Furthermore, many patients experience some adverse physiological reactions during radiotherapy, such as nausea and/or vomiting (Grabenbauer and Holger 2016). Some radiation-induced diseases, such as pneumonia, mucositis, and cardiac disease, are also accompanied by radiotherapy (Atkins et al. 2019; Grabenbauer and Holger 2016; Sato et al. 2018). Therefore, reducing the injury of accidental exposure to radiation and maximizing the effects of radiotherapy on tumors while minimizing radiotoxicity to patients are the ultimate aims of researchers.

Over the past decades, studies ofmicroRNA (miRNA) have revealed a strong association with the radiation response in various cell lines, tissues, and animal models, which provide new insights to avoid the hazards of IR. miRNAs, a class of small non-coding RNAs (about 22 nt), are negative gene regulators at the posttranscriptional level through binding to the 3′-untranslated regions of target mRNAs to inhibit expression (Bartel 2004). miRNAs regulate the cellular response to IR by participating in multiple pathways involved in DNA repair, cell cycle checkpoints, apoptosis, autophagy, and oxidative stress (Gandellini et al. 2014). Accumulating studies have shown that dysregulation of some single miRNAs facilitates the progression of adverse reactions induced by radiation or promotes sensitivity to radiation (Tian et al. 2019; Yan et al. 2018). There is increasing interest for researchers to investigate functional relationships between miRNA expression and IR.

IR alters miRNA expression

Through the development of high throughput sequencing and miRNA databases, many research groups have explored the associations of specific miRNAs with cellular responses to radiation. Their reports have demonstrated that radiation changes miRNA expression significantly. In the serum of baboons, miR-212 showed 48–77-fold upregulation upon 2.5 and 5 Gy irradiation, while miR-342-3p showed 10-fold downregulation (Port et al. 2018, 2016). In the blood of irradiated mice, several members of the miR-17 family (miR-17-5p, -106b-5p, -20a-5p, and -20b-5p) suppressed the response to 2 Gy radiation (Aryankalayil et al. 2018). miR-375-3p was increased significantly in mouse serum after whole body exposure to 7 Gy of X-ray (Chiba et al. 2018). At the organ level, miR-146a-5p was downregulated and miR-467b-5p was upregulated in the IR-exposed mouse thymus (Chen et al. 2016). miR-34c/138 was downregulated, and members of the Let-7 family were upregulated in mice testes upon carbon ion irradiation (He et al. 2018). miR-3037b-5p/34a-5p were upregulated in the irradiated mouse liver after total body irradiation (Lu et al. 2016). In radiotherapy, IR increased the serum miR-34a level in 44 women with breast cancer (Halimi et al. 2016). miR-29a-3p and miR-150-5p were decreased with increasing radiation doses in lung cancer patients (Dinh et al. 2016). In prostate cancer patients, two miRNAs, namely hsa-let-7a-5p and hsa-miR-21a-5p, were upregulated by irradiation (Malla et al. 2018). Taken together, these results indicate that miRNA changes in response to radiation are dependent on the dose, cell type, and disease. Furthermore, in normal thyroid cells (FRTL-5 CL2), miR-10b-5p/199a-3p were downregulated at 1-h post-irradiation and then upregulated after 6 h, which finally returned to the unexposed control expression level at 24-h post-irradiation (Penha et al. 2018). This study indicated that radiation-modulated miRNAs are transient and may have different temporal expression patterns. Thus far, the mechanism underlying how ionizing radiation regulates miRNA expression remains largely unknown and further in-depth studies are needed.

miRNAs regulate important genes related to the cellular radioresponse

miRNAs strongly affect the cellular radioresponse via regulation of vital genes involved in DNA damage repair, cell cycle checkpoints, and apoptosis (Fig. 1). IR destroys DNA structures with ionizing events and the generation of free radicals and reactive oxygen species (ROS). Some miRNAs such as miR-139-5p induced by IRexacerbated accumulation of DNA damage by targeting ROS defense-related gene methionine adenosyltransferase 2 (MAT2A) (Pajic et al. 2018). The first step in triggering the DNA damage response is sensing the DNA damages by ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia (ATR) that activate cyclin-dependent kinase (CHK) and subsequently triggers the signaling pathway leading to checkpoint activation and DNA repair (Awasthi et al. 2016). Cell division cycle 25A (CDC25A) accelerates entry into S phase and promotes mitotic events by activating cyclin-dependent kinase (CDK)-cyclin complexes, while CHK mediates S and G2 phase arrest through phosphorylation of CDC25A, which causes its degradation (Boutros et al. 2007). In this process, many miRNAs repress cell growth by

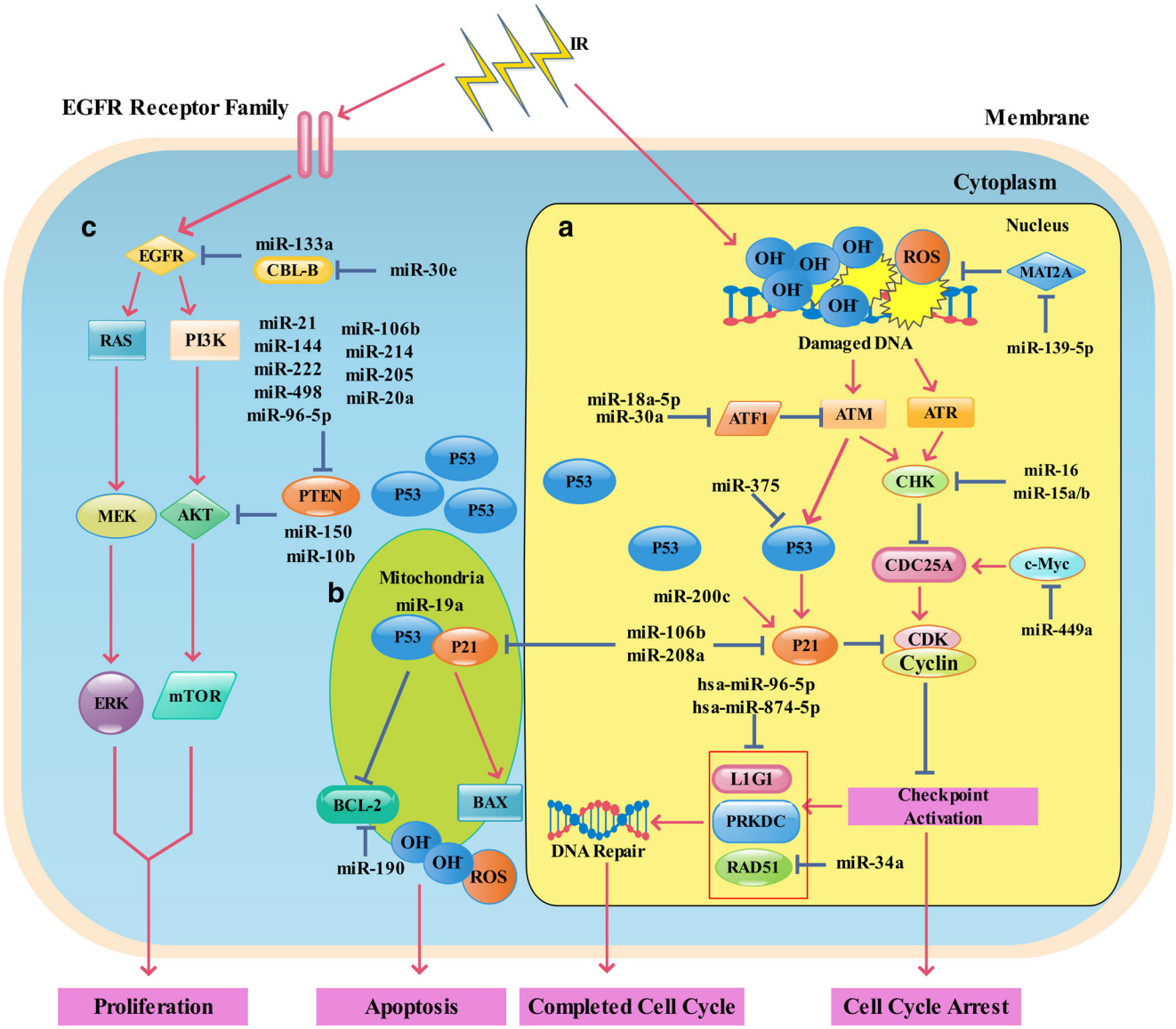

Fig. 1 miRNAs participate in the regulation of key genes related to cellular response to IR. **a** IR-induced damaged DNA is sensed by ATM and ATR. Both of them can trigger activation of CHK and initiate the signaling pathway, leading to Checkpoint activation and DNA repair. Actived CHK degrades CDC25A, and consequently impairs CDK/Cyclin complex that is necessary for transform from G1 to S phase and G2 to M phase. What is more, ATM/P53/P21 is another vital pathway to inhibit cell cycle progress. P53 can be activated by ATM with phosphorylation and subsequently stimulates expression of P21, which is an inhibitor of CDK/Cyclin complex. After activation of checkpoint, if DNA repair goes smoothly, the cell cycle goes on. **b** ATM-activated P53 aggregating in cytoplasm cooperates with P21 and promotes mitochondria to produce reactive oxygen species via inhibition of anti-apoptotic gene BCL-2 and enhance pro-apoptotic gene BAX, ultimately leading to apoptosis. **c** IR is able to activate EGFR and EGFR initiates PI3K/AKT pathway and MAPK pathway to promote cell proliferation. PTEN is an important antagonist of AKT. Its inhibition is closely related to activation of PI3K/AKT pathway and cell proliferation. miRNAs have a great effect on cellular response to IR via negative regulation of genes associated with proliferation, apoptosis, DNA repair, and cell cycle. More information depicted in text

downregulating these factors. miR-30e blocked IR-induced G2/M checkpoint arrest with increased ATM by targeting activating transcription factor 1 (ATF1) that phosphorylates ATM (Guo et al. 2017). Overexpression of miR-18a-5p inhibited the growth of non-small lung cancer xenografts (A549) after radiation exposure by downregulating ATM (Chen et al. 2018). The miR-15 family (miR-15a/b, -16) released radiation-induced G2 arrest and suppressed cell proliferation after irradiation by targeting CHK1 and downregulating B cell lymphoma 2 (BCL-2) in breast cancer cells (Mei et al. 2015). miR-449a enhanced radiation-induced G2/M phase arrest by downregulating Myc proto-oncogene protein (c-Myc) and cell cycle regulator CDC25A in prostate cancer cells (Mao et al. 2016). c-Myc stimulates CDC25A expression, and CDC25A accelerates entry into S phase and promotes mitotic events by activating CDK-cyclin complexes

(Boutros et al. 2007; Galaktionov et al. 1996). Furthermore, ATM/cellular tumor antigen p53 (P53)/cyclin-dependent kinase inhibitor 1A (P21) is another important pathway that activates cell cycle checkpoints. CHK2 activated by ATM phosphorylates P53. The latter accumulates in the nucleus and stimulates downstream P21 expression (Jin and Oh 2019). miR-375 promoted radiosensitivity of HR-HPV (+) cancer cells by decreasing P53 degradation, thereby increasing radiation-induced apoptosis (Song et al. 2015). miR-200c induced G2/M and sub-G1 arrest, decreased the S phase rate in esophageal cancer cells with reduced Cyclin B1 and CDK1, and increased P21 (Zheng et al. 2017). However, miRNAs whose target gene is P21 determine a very different cellular fate. miR-106b enhanced the tumor-initiating cell capacity by directly targeting PTEN and P21 (Zheng et al. 2015b). Radiation-induced miR-208a increased the proliferation and radioresistance of human lung cancer cells by targeting P21 and activating the AKT/mTOR pathway (Tang et al. 2016).

When DNA damages caused by IR activate cell cycle checkpoints, broken DNA strands are repaired mainly by two mechanisms: NHEJ and HR pathway. If DNA damage can be repaired completely, the cell cycle continues, or the cell dies due to apoptosis or mitotic catastrophe (Maier et al. 2016). Overexpression of hsa-miR-96-5p and hsa-miR-874-3p combining with IR decreased the survival of non-small cell lung cancer (NSCLC) cells to a higher extent than that exerted by radiation alone by targeting DNA repair protein RAD51 homolog 1 (RAD51) and DNA-dependent protein kinase catalytic subunit (PRKDC) and leucine-rich repeats and immunoglobulin-like domain protein 1 (L1G1) that are genes involved in HR and NHEJ pathways (Piotto et al. 2018). miR-34a suppressed DNA repair after irradiation and promoted apoptosis of NSCLC cells by targeting RAD51 (Cortez et al. 2015). ATM activates P53 aggregates in the cytoplasm to inhibit anti-apoptotic gene BCL-2, releases pro-apoptotic gene Bcl-2-like protein 4 (BAX) with P21, then enhances the ability of mitochondria to produce ROS (Dogu and Díaz 2009; Kim et al. 2017). Consistent with these findings, miR-208a, whose target gene was P21, upregulated BCL-2 while downregulating BAX (Tang et al. 2016). miR-19a was related to proliferation and metastasis of cervical cancer cells, but inhibition of miR-19a reduces cell proliferation andincreased apoptosis with upregulation of BAX and downregulation of BCL-2 (Wang et al. 2017). A low level of miR-190b and high expression of BCL-2 were found in radioresistant gastric cells, whereas miR-190b mimics reduced the survival rate of gastric cells and sensitized the cells to radiation by downregulation of BCL-2 (Wang and Qiao 2017).

In response to IR, the epidermal growth factor receptor (EGFR) family in the membrane activates and EGFR functions as an anti-apoptotic factor, especially in heterodimers with receptor tyrosine-protein kinase erbB-2 (ERBB2) (Maier et al. 2016). It has been reported that IR-inducible miR-30e promoted glioma cell invasion through EGFR stabilization by directly targeting casitas B-lineage lymphoma B (CBL-B), which increased EGFR abundance (Kwak et al. 2015). EGFR activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway to prevent apoptosis and promote cell proliferation (Fig. 1) (Krieger et al. 2019; Lee et al. 2018). Phosphatase and tensin homolog (PTEN) is an important antagonist of AKT (Zheng et al. 2016). Many miRNAs have been reported to downregulate PTEN to activate the PI3K/AKT pathway, which enhances radioresistance with increased proliferation (Fig. 1) (Duan et al. 2019; Pan et al. 2017; Vahabi et al. 2019; Wu et al. 2018b; Yu et al. 2015a; Zhang and Zhang 2017; Zhang et al. 2015c; Zhou et al. 2015a). miR-150 promoted IR-induced apoptosis in NK/T cell lymphoma cells by directly targeting AKT1 and AKT2 (Wu et al. 2018a), while miR-10b weakened the IR-induced inhibitory effect on reproduction of glioblastoma by targeting p-AKT (Zhen et al. 2016). The mitogen-activated protein kinase (MAPK) pathway activated by EGFR is another pathway that contributes to cell proliferation (Fig. 1). miR-133a was upregulated in radiosensitive patients with esophageal cancer and increased cancer cell apoptosis by targeting EGFR with reduced phosphorylated mitogen-activated protein kinase 1/2 (MEK1/2) and phosphorylated extracellular signal regulated kinase 1/2 (ERK1/2) expression (Yang et al. 2017).

miRNAs have been reported to participate in the regulatory network of radiation autophagy (Fig. 2). Song et al. (2016) have reported that exosomal miR-7-5p was upregulated in human bronchial epithelial cells (BFP2D) after irradiation, which induced autophagy by targeting EGFR with activation of the AKT/mTOR pathway and upregulation of Beclin-1. Cai et al. (2017) found that exosomal miR-7 induced bystander autophagy in lungs after brain irradiation via inhibition of BCL-2. Unlike these miRNAs that induce autophagy, some miRNAs perform converse function about it. For example, miR-216a and miR-17-5p were both downregulated after irradiation. Downregulation of miR-216a and miR-17-5p upregulated the expression of Beclin-1 as a critical autophagic gene, which led to autophagy (Hou et al. 2017; Zhang et al. 2015b).

miRNAs participate in radiation-induced carcinogenesis

Radiation carcinogenesis is regarded as a fateful long-term effect of exposure to radiation. Increasing data have demonstrated alterations of miRNAs in different types of cancer induced by radiation, which indicates their important role in radiation carcinogenesis (Cui et al. 2014; Iizuka et al. 2012; Kim et al. 2016). Bueno et al. (2008) have reported that a chromosomal region (chromosome 12 position 107.4–113.7 Mb enriched with miRNAs) was frequently lost in irradiated T cell lymphomas. In a further study, they found that

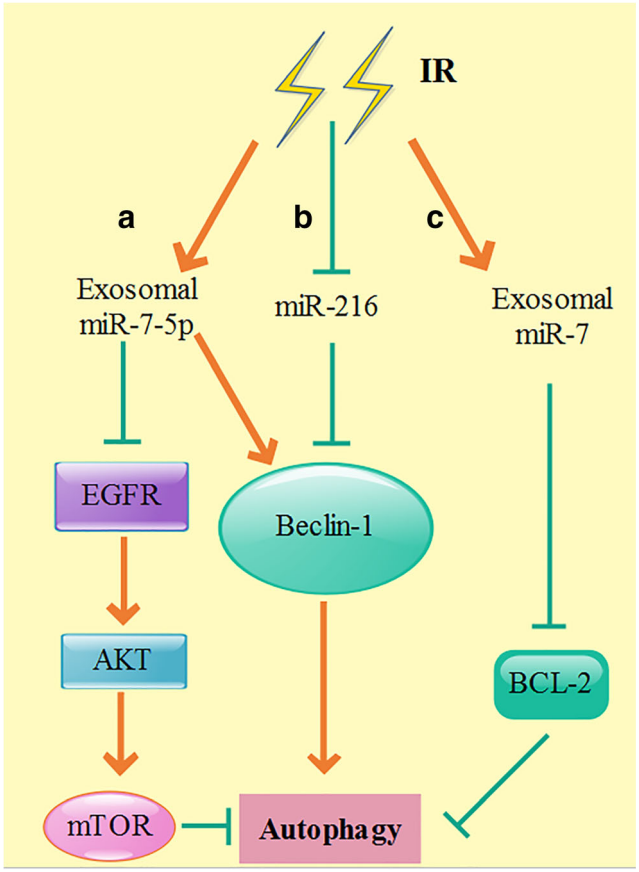

Fig. 2 IR induces autophagy through alternation of miRNAs. **a** Exosomal miR-7-5p upregulated by IR targets EGFR and inactives AKT/mTOR pathway that localizes at downstream of EGFR, leading to process of autophagy. **b** Beclin-1 as a critical autophagic gene, its overexpression regulated by miRNAs results in autophagy. **c** Exosomal miR-7 increased by IR promotes autophagy by targeting BCL-2

miR-203 located in this 7 Mb region was silenced significantly by additional hypermethylation. Silencing of miR-203 enhanced expression of Abelson murine leukemia viral oncogene homolog 1 (ABL1) and break-point cluster region (BCR)-ABL1 that are classic oncogenes extensively characterized in hematopoietic malignancies and both chronic myelogenous and B cell leukemias, respectively. In radiation-induced thymic lymphoma, one of the most classic models of radiation-induced carcinoma, miR-467 was identified as a new oncomiRNA and its overexpression facilitated tumorigenesis by targeting pro-apoptotic gene tumor necrosis factor receptor superfamily member 6 (FAX) and BAX (Gao et al. 2015), while miR-143 was downregulated and its downregulation also promoted radiation-induced thymic lymphoma by targeting B7 homolog 1 (B7H1), which may allow cancer cells to evade the host immune system (Zhao et al. 2017). Additionally, miR-21, the star oncomiRNA, has been reported to perform its pro-tumor function in conjunction with radiation (Liu et al. 2011). Zhang et al. (2019) had identified a functional link between IR-inducible miR-21 and angiogenesis that promotes metastasis, invasion and growth of tumors. Ionizing radiation induced miR-21 overexpression, which in turn downregulated expression of PTEN and finally induced angiogenesis via increased vascular endothelial growth factor A (VEGF) and HIF-1α expression through the PI3K/AKT pathway. This study further verified miR-21 as potent factor in radiation carcinogenesis. IR is capable of amplifying oncomiRNAs that inactivate tumor suppressor genes or restraining anti-oncomiRNAs that target oncogenes, which triggers carcinoma formation (Fig. 3). These studies support the mechanism through which IR acts as a carcinogen to provoke the onset of carcinogenesis from the aspect of miRNA and provide a new insight for radiation oncology.

Modulation of miRNA contributes to improvement of radiosensitivity in tumors

A large number of studies have focused on the role of miRNAs in response to IR in various tumor types (details in Table 1). The findings reveal the association between miRNAs and radiotherapy and possible new treatments for cancer. Especially in the case of inoperable carcinomas such as melanomas, sarcomas, and some tumors with radioresistance (He et al. 2017a; Yang et al. 2018), the importance of targeting modulation of specific miRNAs as a strategy to improve the effect of radiotherapy is evident (Korpela et al. 2015). Members of the Let-7 family and miR-34a have been identified as tumor growth suppressors (Li et al. 2016; Sun et al. 2016). Overexpression of Let-7b sensitized uveal melanoma cells to IR by targeting cyclin D1 (Zhou et al. 2015b). miR-34a directlybound to the 3′-untranslated region of RAD51 involved in DNA double-strand break repair and sensitized lung tumors to radiation (Cortez et al. 2015). Conversely, downregulation of miR-21, which was considered as an oncomiRNA that contributed to angiogenesis, radiosensitized non-small cell lung cancer by increasing PTEN expression (Tang et al. 2019; Zhang et al. 2015a). In addition to regulating pathways related to DNA repair and apoptosis, miRNAs regulate the tumor response to radiation via other mechanisms. miR-449a enhanced radiosensitivity of A549 cells by suppressing lactate dehydrogenase A (LDHA) and glycolysis that is a primitive metabolic pathway easily exploited by cancer cells for energy to grow and spread (Birts et al. 2020; Li et al. 2018c). miR-129-5p repressed radiation-induced autophagy by targeting high-mobility group box-1 protein 1 (HNGB1) in breast cancer, while autophagy was thought to contribute to radioresistance because of its capability to remove ROS and inhibit apoptosis (Li et al. 2018b; Luo et al. 2015). miR-875-5p had the potential to counteract epithelial-to-mesenchymal transition (EMT) to circumvent radiation resistance in prostate cancer by inhibition of the EGFR-zinc finger E-box-binding homeobox 1 (ZEB1) axis (El Bezawy et al.

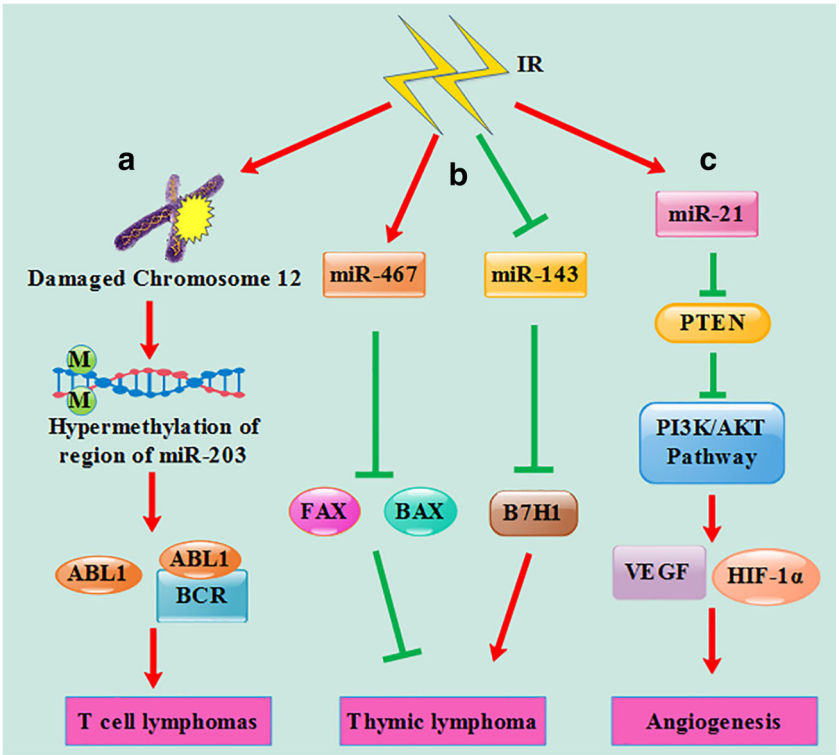

Fig. 3 IR-induced modulation of miRNAs initials carcinogenesis. **a** IR destroys structure of chromosome 12 and causes silence of miR-203 to facilitate carcinogenesis with enhancing expression of oncogene ABL1 and ABL1-BCR. **b** IR increases expression of miR-467 and suppresses expression of miR-143. miR-467 targets pro-apoptotic gene FAX and BAX that inhibit thymic lymphoma, while target gene of miR-143, B7H1, promotes this disease. **c** IR-induced miR-21 activates PI3K/AKT pathway by targeting PTEN, then increases VEGF and HIF-1α level to promote angiogenesis

2017). miR-195/16 family improved the effect of radiotherapy via blocking the programmed death-1 ligand 1(PD-L1) immune checkpoint along with activation of T cells in the tumor microenvironment (Tao et al. 2018). Therefore, specific miRNAs determine the tumor response to radiation via multiple mechanisms. Accordingly, manipulation of their expression either by mimicking or inhibiting has attracted great interest for miRNA-based interventions to improve radiotherapy effectiveness (Gandellini et al. 2014). Thus, it is possible to use miRNAs as a potential adjuvant for radiotherapy.

miRNAs involved in radiotherapy-related toxicity

Apart from tumor sensitivity to radiation, miRNAs are closely related to the side effects induced by radiotherapy. They act as mediators to affect bystander effects through exosomes, which increases the risk of normal cellular injury and the likelihood of secondary cancer after radiotherapy (Yahyapour et al. 2018). Radiation-induced miR-21 could be transferred to recipient or bystander cells through exosomes, which resulted in bystander-like micronucleus formation, oxidative stressand DNA damage (Tian et al. 2015; Xu et al. 2015; Yin et al. 2015). However, unlike miR-21, miR-495acted as protector against radiation-induced bystander effects. Its overexpression produced fewer necrotic foci in adjacent, non-irradiated tissue after tumors received local irradiation compared with the low expression group (Fu et al. 2016). Lung fibrosis is the most serious side effect of lung cancer radiotherapy on normal tissue. IR-induced miR-21 was sufficient to promote the radiation-induced pulmonary fibrotic response, concurrent with EMT and collagen deposition, while miR-29 had a converse function to repress type I collagen against radiation-induced fibrosis (Kwon et al. 2016; Yano et al. 2017). miR-1, -21, -208, -133, -29, -199b, -221, -222, and -155 were dysregulated in radiation-induced heart diseases (Kura et al. 2017). miR-200c was reported to radiation-induced oral mucositis, which almost happened in the patients receiving radiotherapy for head and neck cancer. Inhibition of miR-200c suppressed expression of pro-inflammatory cytokines transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α) and interleukin-1α (IL-1α), and increased the production of molecules associated with EMT (snail homologue 1(Snail), vimentin, ZEB1, and polycomb complex protein BMI-1 (Bmi-1)) (Tao et al. 2019). Furthermore, abdominal and pelvic radiotherapies have been reported to impair distant cognitive functions, whereas inhibition of miR-34a-5p and restoring expression of its target gene, brain-derived neurotrophic factor (Bndf), relieved this condition effectively (Cui et al. 2017).

miRNAs may serve as novel biomarkers for accidental and professional exposure to IR

Over three decades, a growing body of evidence has shown that miRNAs have the potential to be useful diagnostic and prognostic biomarkers in clinic. miRNAs are stable and

Table 1 The miRNAs and the relationship between miRNAs and radiosensitivity in multiple cancers

Cancers	miRs	Response to IR	Refs
Breast cancer	miR-144	Resistance	Yu et al. (2015a)
	miR-200c	Sensitivity	Sun et al. (2015)
	Let-7d	Sensitivity	Sun et al. (2016)
Prostate cancer	miR-145	Sensitivity	Gong et al. (2015); Xue et al. (2015)
	miR-205	Sensitivity	Wang et al. (2016b); Xu et al. (2016)
	miR-30a	Sensitivity	Xu et al. (2016)
	miR-144	Sensitivity	Gu et al. (2016)
	miR-124	Sensitivity	Gu et al. (2016)
Lung cancer	miR-21	Resistance	Jiang et al. (2017); Liu et al. (2014); Song et al. (2017); Zhang et al. (2015a)
	miR-155	Resistance	Lv et al. (2016)
	miR-34a	Sensitivity	Cortez et al. (2015); He et al. (2017b)
	miR-9	Sensitivity	Wei et al. (2019)
	miR-18a	Sensitivity	Shen et al. (2015)
	miR-124	Sensitivity	Hao et al. (2017)
	miR-200c	Sensitivity	Zhai et al. (2016)
	miR-339-5p	Sensitivity	Wang et al. (2018)
	miR-30a	Sensitivity	Guo et al. (2017)
Nasopharyngeal cancer	miR-21	Resistance	Zhu et al. (2015)
	miR-203	Sensitivity	Qu et al. (2015)
	miR-222	Resistance	Wu et al. (2018b)
	miR-9	Resistance	Zheng et al. (2015a)
	miR-124	Sensitivity	Zhang et al. (2017)
Colorectal cancer	miR-155	Resistance	Khoshinani et al. (2017)
	miR-222	Resistance	Khoshinani et al. (2017)
	miR-185	Sensitivity	Afshar et al. (2018)
	Let-7e	Sensitivity	Samadi et al. (2019)
Cervical cancer	miR-145	Sensitivity	Ye et al. (2015)
	miR-18a	Sensitivity	Liu et al. (2015)
	miR-125a	Sensitivity	Pedroza-Torres et al. (2018)
	miR-375	Sensitivity	Song et al. (2015)
Esophageal cancer	miR-21	Resistance	Li et al. (2018a)
	miR-205	Resistance	Pan et al. (2017)
	miR-124	Sensitivity	Zhang et al. (2016)
	miR-200c	Sensitivity	Zheng et al. (2017)
	miR-339-5p	Resistance	Luo et al. (2019)
Liver cancer	miR-34a	Sensitivity	Li et al. (2016)
	miR-203	Sensitivity	Shao et al. (2018)

steadily exist in multiple biofluids such as plasma, serum, blood, and urine, and even in tissues fixed in formalin (Duan et al. 2020; Enelund et al. 2017; Ma et al. 2016a). These advantages meet the criteria of becoming a biomarker that is stable post-IR exposure and allows repeated testing in a minimally invasive manner. Most miRNAs are specific to tissues and evolutionarily conserved across species (Huang 2017; Vishnoi and Rani 2017). In the case of human acute radiation syndrome caused by accidental or deliberate exposure to radiation, it is of particular importance for exposed person to be rapidly and accurately classified into definable susceptible population. Małachowska et al.

(2020) conducted experiments in nonhuman primates that share > 95% genetic information with humans. They revealed that the combination of serum concentrations of miR-133b/215/375 was able to classify irradiated versus unirradiated animals and two miRNAs (miR-30a and miR-126) were identified as predictors of radiation-induced fatality in nonhuman primates. Another study suggested that serum miRNAs could serve as functional dosimeters for early indication after hematopoietic injury caused by radiation (Acharya et al. 2015). In this study, miR-130a-3p was upregulated, whereas miR-150-5p, -142-5p, -706, and -342-3p expressions were significantly decreased after exposure to total body irradiation dose of 2 Gy. Furthermore, differential expression of five miRNAs (miR-136-5p, -17-3p, -126-3p, -322-3p, and -34b-3p) effectively distinguished the high sublethal group (6.5 Gy) from the low-dose sublethal group (2 Gy), and differential expression of miR-30a-3p/30c-5p distinguished lethal (8 Gy) and sublethal (6.5 Gy) groups. In addition to biomarkers to assess radiation injury, miRNAs may be applied as clinical biomarkers in the prediction and prognosis of radiotherapy effects (details in Table 2). Some miRNAs indicate sensitivity or resistance to IR in patients with various kinds of cancers, who received radiotherapy previously (details in Table 2) (Hoey et al. 2018; Wang et al. 2019; Wei et al. 2017). These miRNAs probably could be used as biomarkers for radiosensitivity or radioresistance. Furthermore, miRNAs have a close relationship with the prognosis of post-radiotherapy (details in Table 2) (Bell et al. 2015; Hoey et al. 2018; Ma et al. 2016b). In esophageal squamous cell carcinomas, miR-16 showed significantly higher expression in patients with good outcomes post-radiotherapy (Yu et al. 2015b). Head and neck carcinoma patients with high expression of miR-15b-5p showed less locoregional release and longer survival compared with patients who showed low expression (Ahmad et al. 2019). In the late effect of radiotherapy, miR-125a was closely related to induction of pneumonitis in lung cancer patients who received radiotherapy (Quan et al. 2018), and low Ku80 expression and high miR-99a expression were promising predictors of rectal bleeding after radiotherapy for prostate cancer (Someya et al. 2015). In radiation-induced renal tubular injury, urinary hsa-miR-1224 was considered as a potential early responder to nephropathy,

Table 2 miRNAs related to clinical outcome of radiotherapy in different cancer patients

Cancers	miRs	Clinical outcome of radiotherapy in patients	Refs
Non-small cell lung cancer	miR-208a/21-5p	Highly expressed in radioresistant patients.	Song et al. (2017); Tang et al. (2016)
	miR-125a	Associated with induction of radiation-induced pneumonitis.	Quan et al. (2018)
	miR-95	Closely related to recurrent after radiotherapy.	Ma et al. (2016b)
Prostate cancer	miR-4516/601	Associated with biochemical failure of post-salvage radiotherapy.	Bell et al. (2015)
	miR-99a	Associated with rectal bleeding after radiotherapy.	Someya et al. (2015)
	miR-106a	Overexpressed in radioresistant cancer cell and related to biochemical recurrence within five years after prostatectomy.	Hoey et al. (2018)
Esophageal cancer	miR-133a/27a	Highly expressed in radiosensitive patients.	Wang et al. (2019); Yang et al. (2017)
	miR-16	Highly expressed in patients with good outcome at post-radiotherapy	Yu et al. (2015b)
Head and neck carcinoma	miR-15b-5p	Associated with less locoregional release and longer survival after intensity-modulated radiotherapy	Ahmad et al. (2019)
Leukemia	miR-1224	Early responder in radiation-induced renal tubular injury	Bhayana et al. (2017)
	miR-21	Late responder in radiation-induced renal tubular injury	Bhayana et al. (2017)
Nasopharyngeal carcinoma	miR-24	Associated with recurrent and sensitize cancer to IR	Wang et al. (2016a)
Cervical cancer	miR-18a/125a/145	Highly expressed in radiosensitive patients	Liu et al. (2015); Pedroza-Torres et al. (2018); Wei et al. (2017)

while urinary hsa-miR-21 was a late responder (Bhayana et al. 2017). Taken together, miRNAs as biomarkers may facilitate precise dose escalation and prediction of prognosis during radiotherapy. These studies support that miRNAs have strong prospects in the clinic, although the results of current studies are too heterogeneous and preliminary.

Perspectives

Overall, the current research has shown that miRNAs are able to affect the mechanisms and pathways involving to cellular responses to IR, although the studies are somewhat divergent and the heterogeneous results require further systematic analysis for normalization. Currently, miR-34a that has been clearly identified as a tumor suppressor has reached the clinical trial stage, and various nanoparticles as miRNA carriers have emerged (Beg et al. 2017; Bejerano et al. 2018; Campani et al. 2016; Ren et al. 2019). These studies show that miRNA therapeutics have a good perspective in radiation oncology (Rancoule et al. 2016; Rupaimoole and Slack 2017). Moreover, with progressively deepening of our understanding of the regulatory mechanisms of miRNAs during exposure to ionizing radiation, miRNAs may be accepted as biomarkers at the levels of proteins in the near future, which will be not only used to rapidly classify injury from radiation exposure, but also treatment responses, untoward reactions, and customized radiotherapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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