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REVIEW

MicroRNAs and Their Impact on Radiotherapy for Cancer

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Resistance to radiation is considered to be an important reason for local failure after radiotherapy and tumor recurrence. However, the exact mechanisms of tumor resistance remain poorly understood. Current investigations of microRNAs as potential diagnostic and therapeutic tools for cancer treatment have shown promising results. With respect to radiotherapy resistance and response, there is now emerging evidence that microRNAs modulate key cellular pathways that mediate response to radiation. These data suggest that microRNAs might have significant potential as targets for the development of new therapeutic strategies to overcome radioresistance in cancer. This review summarizes the current literature pertinent to the influence of microRNAs in the response to radiotherapy for cancer treatment, with an emphasis on microRNAs as novel diagnostic and prognostic markers, as well as their potential to alter radiosensitivity.

INTRODUCTION

Radiation therapy induces a complex cellular response when treating cancer cells and leads to changes in the expression of numerous genes involved in key cellular processes such as cell signaling, proliferation and damage response (*1, 2*). Cellular damage after radiotherapy occurs either directly by disruption of DNA integrity or indirectly by free radicals and reactive oxygen species that cause DNA double-strand breaks (DSBs) (*2–4*). As a result, complex signaling pathways are activated and DNA damage response is triggered. Cell death occurs from a failure to repair radiation-induced damage (*1, 5*).

Several factors have been shown to influence response to radiation, including tumor origin, vascular supply/extent of hypoxia, cell-cycle phase and the repopulation potential of surviving cells (*6, 7*). However, the main factor influencing response to radiotherapy seems to be the intrinsic radioresistance of tumor cells. Despite increasing knowledge about the effects of radiation on biochemical pathways, the exact mechanisms of intrinsic radioresistance remain unclear. To date, it has been reported that a number of key cellular features appear to play a role in the development of intrinsic radioresistance, including overexpression of DNA repair proteins (*8*), modifications of signaling pathways (*9*), angiogenesis (*10*) and the presence of cancer stem cells (*11*).

Resistance to radiotherapy remains a serious obstacle to successful cancer therapy and directly impacts clinical outcomes (*12*). Unfortunately, there are currently no reliable clinical or molecular markers available that help estimate or predict response (*13*). In this context, microRNAs (miRNAs), a class of regulatory molecules that play an essential role in various physiological and pathological processes such as cancer development, might be promising candidates (*14, 15*). miRNAs are considered to be highly specific biomarkers with potential for clinical applications, and their expression has been shown to correlate with tumor occurrence, development, clinical prognosis and therapeutic efficacy (*3, 14*). Beyond their use as diagnostic or prognostic biomarkers, the manipulation of miRNAs may offer new opportunities in the treatment of cancer . Recent studies have shown that miRNAs play an important role in radiation-induced gene expression, cell-signaling events and regulation of damage-response pathways (*16, 17*). Most interestingly, miRNAs have been shown to modulate radiosensitivity (*1, 5*). Therefore, miRNAs might be promising candidates for the assessment and monitoring of radiosensitivity of tumors, as well as modulation of response to radiation treatment (*18*).

METHODS

A PubMed search was performed using combinations of the following keywords: miRNA, microRNA, biomarker, radiotherapy, radioresistance and radiosensitivity. Articles that met the criteria were identified (number of articles found are inticated in parentheses):

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miRNA and radiotherapy (324); microRNA and radiotherapy (341); miRNA and radioresistance (76); microRNA and radioresistance (70); miRNA and radiosensitivity (197); microRNA and radiosensitivity (203); radiation and miRNA and biomarker (117); radiation and microRNA and biomarker (123); and circulating and miRNA and radiation (19). Relevance was further determined by screening the abstracts and text of the entire published article, as necessary. Reference lists from relevant articles were also searched for additional literature. Data were extracted from the article or, if only available in the abstract, from there. This method was applied until the beginning of June 2015.

A narrative review of relevant literature was conducted to identify and summarize evidence that miRNAs might be useful as biomarkers to predict and monitor response to radiotherapy, and also to determine the potential for manipulation of miRNAs to modulate radiotherapy response. The underlying mechanisms of action by which miRNAs might affect sensitivity to radiotherapy were also reviewed.

miRNAS AS POTENTIAL NEW CLINICAL MARKERS FOR DIAGNOSIS, PROGNOSIS AND TREATMENT

miRNAs have potential for use as clinically relevant biomarkers of response to radiotherapy, and also to modulate radiotherapy response.

MiRNAs as Predictors of Response to Radiotherapy

Given the variety of patient responses to radiation treatment, the ability to predict response versus non-response would allow treatment to be individualized, thereby helping patients avoid unnecessary risks of toxicity and side effects if they are unlikely to benefit from radiotherapy (*19, 20*). To distinguish between responders versus non-responders using miRNA profiling methods, distinct differences in miRNA expression profiles of tumors for each patient group must be present. Unfortunately, most clinical and experimental studies investigating miRNAs and their correlation to treatment response include patients that have undergone combined chemo-radiotherapy, making it difficult to identify miRNAs that specifically correlate with only radiotherapy response. However, in a limited number of recent studies using cancer cell lines or clinical samples, it has been reported that miRNAs investigated in the setting of radiotherapy alone have shown promising early results (*21*).

For example, using samples from patients with non-small cell lung cancer, Wang *et al*. demonstrated that 5 miRNAs were significantly upregulated in radiosensitive tumors (let-7a; miR-126, -128b, -451, -495) and 7 miRNAs were downregulated compared to controls (miR-15b; -17-5p, -19b, -21, -22, -106b, -130a) (*22*). In another study, higher miR-18a expression levels were observed in tumors from patients who failed to respond to radiation treatment, compared to responders ($P = 0.019$) (*23*).

In the context of head and neck tumors, Qu *et al*. established a radiation-resistant nasopharyngeal carcinoma cell line and reported 8 miRNAs to be differentially expressed compared to the parental cells (upregulation of let-7g, miR-205; -224; downregulation of miR-18a; -19b, -24, -93, -103), with the most significant expression changes between resistant and sensitive cells seen for miR-205 (*24*). In another published study, miR-196a was shown to be the most upregulated miRNA of 41 differentially expressed miRNAs in squamous cell carcinoma tumor samples from non-responders compared to responders (*25*).

Similar results have been demonstrated in biopsies from squamous cervical carcinoma, with miR-16-2, -18a, -23a, -30, -221 and -378 downregulated in samples from radiation-resistant tumors sampled six months after completion of radiation treatment, while miR-21 and miR-181a were found to be upregulated. However, the significance of this study is limited, since patients underwent concurrent cisplatin chemotherapy (*12*). Table 1 summarizes the published studies that suggest miRNAs have a potential role as predictors of radiotherapy response.

MiRNAs to Monitor Response to Radiotherapy

As radiotherapy is usually delivered over several weeks, early identification of patients who are failing to respond might provide an opportunity to avoid ineffective treatment or delays in moving to alternative treatment options. For ''real-time'' assessment of radiotherapy response using miRNA profiling methods, miRNA expression should change in a characteristic manner across the course of successful radiotherapy treatment. Some recently published studies using miRNA profiling techniques, including microarrays, real-time quantitative PCR and next-generation deep sequencing, have revealed that exposure to radiation triggers specific changes in miRNA expression (*26*).

General changes in miRNA expression under radiotherapy. The majority of published studies have focused on (benign or malignant) cell lines or cancer tissue biopsies, and investigated whether radiation exposure is associated with characteristic changes to miRNA expression profiles (*5, 27–31*). In benign cells, miRNA expression has been shown to be significantly impacted by ionizing radiation (*27, 28*). For example, in endothelial cells, radiation induced upregulation of five miRNAs (let-7g, miR-16; -20a, -21, -29c) and downregulation of six (miR-18a; -125a, -127, -148b, -189, -503) (*28*).

Similar results have been demonstrated in cancer cell lines. Niemoeller *et al*. showed that radiation exposure led to 2–3-fold changes in the expression levels of various miRNAs, such as let-7i, miR-24-1, miR-151-5p and miR-1285 in different cancer cell lines (*29*). Significantly, certain miRNAs have been identified to consistently show characteristic changes postirradiation across a range of different cancers. For example, expression of several members of the let-7 family, a well-known tumor suppressor and regulator of the K-Ras oncogene, were found to be affected by radiation exposure (*29, 30, 32–35*). Most members of the let-7 family (except let-7g) have been found to be downregulated in irradiated fibroblasts (*33*), lung cancer cells (*30*) or colon cancer cells (*35*). However, in irradiated glioma and squamous cell carcinoma cell lines

TABLE 1
miRNAs as Potential Predictors of Response to Radiotherapy

miRNA	Up/downregulation vs. control[a]	Correlation with radioresponse	Cancer type	Specimen (dose)	Targets	Ref.
let-7a	↑	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
let-7g	↑	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	-	(*24*)
miR-15b	↓	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-17-5p	↓	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-18a	↑	↑ Resistance	Lung cancer	Resected lung samples (N.A.); cell lines (10 Gy)	-	(*23*)
	↓	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	-	(*24*)
miR-19b	↓	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
	↓	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	-	(*24*)
miR-21	↓	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy); cell lines (0–8 Gy)	-	(*22*)
miR-22	↓	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-24	↓	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	-	(*24*)
miR-93	↓	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	-	(*24*)
miR-103	↓	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	-	(*24*)
miR-106b	↓	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-126	↑	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-128b	↑	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-130a	↓	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-181a	↑	↑ Resistance	Cervical carcinoma	Biopsies (45 Gy); cell lines (0–8 Gy)	PRKCD[b]	(*12*)
miR-196a	↑	↑ Resistance	Squamous cell carcinoma of the head and neck	Tissue samples	ANXA1[c]	(*25*)
miR-205	↑	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	PTEN[c]	(*24*)
miR-224	↑	↑ Resistance	Nasopharyngeal carcinoma	Cell lines (0–6 Gy)	-	(*24*)
miR-451	↑	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)
miR-495	↑	↑ Sensitivity	Lung cancer	Resected lung samples (60 Gy)	-	(*22*)

Note. PRKCD = protein kinase C delta type; ANXA1 = annexin A1; PTEN = phosphatase and tensin homolog deleted on chromosome 10; NA = Not available.

[a] Up-/downregulation (↑↓) of miRNA compared to respective control.

[b] Assessment of (potential) targets Targetscan research.

[c] Assessment of (potential) targets using luciferase assay.

some members of the let-7 family are upregulated (*29, 34*). Another two miRNAs, miR-21 and miR-34, are consistently upregulated in various benign and malignant cell lines after irradiation (*28, 34, 36–38*).

Only two studies have extended the cell-line outcomes to the clinical setting and investigated miRNA responses in tissues from patients undergoing radiotherapy. In irradiated gastric cancer samples, expression of 18 miRNAs were

altered more than 1.5-fold (upregulation of miR-138-1 and mir-637; downregulation of let-7a, and miR-24-1, -141, -300, -377, -423-3p, -485-3P, -490-5p, -498, -615-3p, -625, -642, -657, -659 and -943) compared to nonirradiated samples (*39*). In nasopharyngeal carcinoma tissues, qRT-PCR revealed upregulation of miR-205 after irradiation, and this was consistent with the authors' *in vitro* data, which showed miR-205 to be upregulated in radioresistant cells (*24*).

Liquid biopsies: the future of molecular diagnostics. Recent studies have also detected so-called ''circulating miRNAs'' in blood samples. These circulating miRNAs, which are present in stable forms in the blood stream, might be detectable as clinical biomarkers (*40*). Radiation-induced changes in blood-based miRNA expression profiles have recently been reported. In the context of myeloablative fractionated exposures before autologous or allogenic stem cell transplants, expression levels of 45 miRNAs, including miR-17; -21, -101, -126 and -148b, have been found to significantly increase compared to preirradiation control samples in mantle cell lymphoma, acute myelogenous leukemia and acute lymphoblastic leukemia (*41*).

Analysis of miR-21 expression levels in the serum of breast cancer patients at different treatment time points revealed significantly increased miR-21 levels after radiotherapy in those individuals who had received chemotherapy five weeks before radiation treatment ($P < 0.001$) (*42*). In addition, high plasma expression levels of miR-142-3p, -186-5p, -195-5p, -374b-5p and -574-3p after the second fraction of radiotherapy were shown to correlate with a poorer prognosis in patients with head and neck squamous cell carcinoma (*43*). However, these patients also underwent concurrent chemotherapy, which might also influence the miRNA expression levels. Finally, consistent with observations made about miR-34 expression in cell lines and cancer tissue biopsies, serum levels of this miRNA were shown to be elevated in irradiated mice compared to nonirradiated controls (*44*).

Changes in miRNA expression profiles compared to radiotherapy response. Only one published study addressed the question of radiation response compared to changes in miRNA expression profiles. miRNA profiling of a (radioresistant and radiosensitive) esophageal adenocarcinoma cell line identified 11 miRNAs with altered expression levels after irradiation, and miR-31 was significantly downregulated in the radioresistant cells (*45*). miR-31 expression was subsequently analyzed in endoscopic esophageal cancer biopsies collected before commencement of neoadjuvant therapy, and increased miR-31 levels in these biopsies were found in the patients with a complete pathologic response. However, because the clinical samples were collected from individuals who received combined chemo-radiotherapy, the relevance of these results to the setting of radiotherapy alone is probably limited.

MiRNAs as Modulators of Response to Radiotherapy

While miRNAs have potential as diagnostic and prognostic markers in the clinical setting, another important question is whether these molecules provide a new opportunity for cancer treatment. Theoretically, manipulation of miRNA levels should result in changes in the expression of genes critical to radiation response, thereby altering radiation sensitivity. There is now growing evidence that modulation of miRNA levels by either enhancing or suppressing the expression of certain miRNAs affects radioresistance in some human tumors. For example, *in vitro* manipulation of levels of members of the let-7 family and miR-21, miR-181a, miR-221 and miR-222 has been shown to impact response to radiotherapy in head and neck squamous cell cancers, uveal melanoma, glioma and neuroblastoma, gastrointestinal tumors (esophageal, gastric, colorectal and liver), gender-specific tumors (breast, cervical and prostate cancer), lung cancer, renal cell cancer and lymphoma (see Table 2 for details on the effects of up-/downregulation of different miRNAs on radiosensitivity in *in vitro* studies). Initial *in vivo* studies have confirmed the *in vitro* findings that the let-7 family, miR-101, miR-145, miR-181a, miR-185, miR-210 and miR-381 affect radiosensitivity in melanoma, glioma, cervical cancer, esophageal cancer, renal cell cancer and hepatoma (Table 3).

MECHANISMS OF ACTION

As miRNAs act by binding to messenger RNA to regulate their translation, miRNAs are involved in the regulation of numerous relevant cellular functions, including DNA damage response and important signaling pathways such as the apoptosis pathway. The impact of miRNAs and targets relevant to radiation response is summarized in Fig. 1.

MiRNAs Modulating DNA Damage Response

Radiation-induced cell death is at least in part caused by miRNA-based repression of pathway components of the damage response, resulting in an impaired ability to detect DNA damage (*1, 21*). One of the most relevant mechanisms of action of radiotherapy is the initiation of DSBs (*5*). Consequently, cellular pathways and repair mechanisms such as homologous recombination and non-homologous end joining are activated by different ''damage sensors'' like ATM (ataxia-telangiectasia mutated) that trigger the DNA repair system (*21*). Efficient repair can lead to radioresistance, which frequently prevents successful treatment (*6*). Several miRNAs appear to modulate and regulate these DNA repair mechanisms. For example, in cervical cancer cell lines, upregulation of miR-18a decreases the ATM level and attenuates efficient DSB repair after radiotherapy (*46*). Two further examples of interaction between miRNAs and the DSB repair machinery by ATM modulation are miR-101 and miR-421. These miRNAs have

TABLE 2
Effect of Up-/Downregulation of Different miRNAs on Radiosensitivity in *In Vitro* Studies

Cancer type and subtype	MiRNA	Regulation	Correlation with response	Dose	Possible targets	Refs.
Head and neck tumors						
Squamous cell carcinoma	miR-196a	↑	↑ Resistance	0–2 Gy	ANXA1	(*25*)
Oral squamous cell carcinoma	miR-125b	↑	↑ Sensitivity	0–8 Gy	ICAM-2	(*66*)
Nasopharyngeal carcinoma	miR-185-3p	↑	↑ Sensitivity	6 Gy	WNT2B	(*71*)
	miR-205	↑	↑ Resistance	10 Gy	PTEN	(*24*)
	miR-324-3p	↑	↑ Sensitivity	60 Gy	WNT2B	(*72*)
Uveal melanoma	let-7b	↑	↑ Sensitivity	0–9 Gy	Cyclin D1	(*73*)
Glioma	miR-7	↑	↑ Sensitivity	2–8 Gy	EGFR-PI3K-Akt	(*49*)
	miR-101	↑	↑ Sensitivity	2–8 Gy	DNA-PKcs, ATM	(*47*)
	miR-181a	↑	↑ Sensitivity	0–35 Gy	Bcl-2	(*74*)
	miR-221; miR-222	↓	↑ Sensitivity	2–6 Gy	PTEN	(*57*)
Neuroblastoma	miR-421	↑	↑ Sensitivity	0–10 Gy	ATM	(*48*)
Gastrointestinal tumors						
Esophageal	miR-21	↓	↑ Sensitivity	0–8 Gy	PTEN (PI3K-Akt)	(*60*)
	miR-22	↑	↑ Sensitivity	0–10 Gy	-	(*75*)
	miR-31	↑	↑ Sensitivity	2 Gy	DNA repair genes	(*45*)
	miR-381	↑	↑ Sensitivity	0–8 Gy	CTNNB1, LEF1, CDK1, XIAP, CXCR4	(*76*)
Gastric	miR-221; miR-222	↓	↑ Sensitivity	0–6 Gy	PTEN (p-Akt)	(*58*)
	miR-451	↑	↑ Sensitivity	0–4 Gy	MIF	(*77*)
Colorectal	miR-100	↑	↑ Sensitivity	0–8 Gy	Apoptosis-related proteins	(*55*)
	miR-124	↑	↑ Sensitivity	0–8 Gy	PRRX1	(*78*)
	miR-221	↓	↑ Sensitivity	0–8 Gy	PTEN	(*54*)
	miR-451	↑	↑ Sensitivity	0–4 Gy	MIF	(*77*)
Hepatoma	miR-210	↓	↑ Sensitivity	8 Gy	AIFM3	(*79*)
Gender-specific tumors						
Breast	miR-7	↑	↑ Sensitivity	2–8 Gy	EGFR-PI3K-Akt	(*49*)
	miR-15	↑	↑ Sensitivity		G_2 checkpoints	(*80*)
	miR-200c	↑	↑ Sensitivity	0-8 Gy	TBK1, autophagy	(*53, 81*)
	miR-221; miR-222	↓	↑ Sensitivity	2-6 Gy	PTEN	(*57*)
Cervical	miR-18a	↑	↑ Sensitivity	-	ATM	(*46*)
	miR-145	↑	↑ Sensitivity	0–8 Gy	HLTF	(*82*)
	miR-181a	↑	↑ Resistance	0–8 Gy	PRKCD	(*12*)
Prostate	miR-521	↑	↑ Sensitivity	0–6 Gy	CSA, MnSOD	(*37*)
Other types						
Lung	let-7	↑	↑ Sensitivity	2–6 Gy	let-60/RAS, DDR	(*30*)
	let-7a			0–8 Gy	K-Ras	(*61*)
	miR-7	↑	↑ Sensitivity	2–8 Gy	EGFR-PI3K-Akt	(*49*)
	miR-9	↑	↑ Sensitivity	2 Gy	NF-κB1	(*70*)
	miR-18a	↓	↑ Sensitivity	0–10 Gy	-	(*23*)
	miR-21	↓	↑ Sensitivity	0–8 Gy	PTEN	(*59, 64*)
	miR-34b	↑	↑ Sensitivity	4–12 Gy	-	(*83*)
	miR-101	↑	↑ Sensitivity	2–8 Gy	DNA-PKcs, ATM	(*47*)
	miR-126	↑	↑ Sensitivity	0–8 Gy	PI3K-Akt	(*22*)
	miR-221; miR-222	↓	↑ Sensitivity	2–6 Gy	PTEN	(*57*)
	miR-449a	↑	↑ Sensitivity	10 Gy	-	(*84*)
	miR-1323	↑	↑ Resistance	-	PRKCD	(*85*)
Renal cell	miR-185	↑	↑ Sensitivity	4 Gy	ATR	(*86*)
Non-Hodgkin lymphoma	miR-148b	↑	↑ Sensitivity	2 Gy	-	(*67*)
Mantle cell lymphoma	miR-17-92	↑	↑ Resistance	0–4 Gy	PTEN	(*87*)

Note. ANXA1 = annexin A1; ICAM-2 = intercellular adhesion molecule-2; PTEN = phosphatase and tensin homolog deleted on chromosome 10; MIF = macrophage migration inhibitory factor; DNA-PKcs = DNA-dependent protein kinase catalytic subunit; ATM = ataxia-telangiectasia mutated; DDR = DNA damage response. PRKCD = protein kinase C delta type. TBK1 = TANK-binding kinase 1; CSA = Cockayne syndrome protein A, NF-κB1 = nuclear factor kappa-light-chain-enhancer of activated B cells; MnSOD = manganese superoxide dismutase; HLTF = helicase-like transcription factor; AIFM3 = apoptosis-inducing factor mitochondrion-associated 3; ATR = ataxia telangiectasia and Rad3-related protein.

TABLE 3
Effect of Up-/Downregulation of Different miRNAs on Sensitivity to Radiotherapy in *In Vivo*/Xenograft Studies

MiRNA	Regulation	Correlation with response	Animal model	Dose	Possible targets	Refs.
let-7	↑	↑ Sensitivity	*C. elegans*	200/400 Gy	let-60/RAS, DDR	(*30*)
let-7b	↑	↑ Sensitivity	Uveal melanoma (mice)	12/18 Gy	Cyclin D1	(*73*)
miR-181a	↑	↑ Resistance	Cervical (mice)	16 Gy	PRKCD	(*12*)
miR-101	↑	↑ Sensitivity	Glioma/lung cancer (mice)	10 Gy	DNA-PKcs, ATM	(*47*)
miR-145	↑	↑ Sensitivity	Cervical (mice)	24 Gy	HLTF	(*82*)
miR-381	↑	↑ Sensitivity	Esophageal (mice)	5 Gy	CTNNB1, LEF1, CDK1, XIAP, CXCR4	(*76*)
miR-181a	↑	↑ Resistance	Cervical (mice)	16 Gy	PRKCD	(*12*)
miR-185	↑	↑ Sensitivity	Renal cell (mice)	4 Gy	ATR	(*86*)
miR-210	↓	↑ Sensitivity	Hepatoma (mice)	8 Gy	AIFM3	(*88*)

Note. DDR = DNA damage response; PRKCD = protein kinase C delta type; DNA-PKcs = DNA-dependent protein kinase catalytic subunit; ATM = ataxia-telangiectasia mutated; HLTF = helicase-like transcription factor; ATR = ataxia telangiectasia and Rad3-related protein; AIFM3 = apoptosis-inducing factor mitochondrion-associated 3.

been shown to influence ATM expression, and ectopic expression/overexpression enhances radiosensitivity in neuroblastoma cell lines (miR-421) (*47, 48*). Other miRNAs, such as miR-7, miR-101 and miR-182, have been shown to target transcripts of DSB repair genes such as BRCA1 (breast cancer 1) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs), respectively, and to radiosensitize cells *in vitro* as well as in xenograft models (*47, 49, 50*). In a panel of human cancer cells, overexpression of miR-7, for example, resulted in downregulation of EGFR and Akt, which was associated with decreased phosphorylation of DNA-PKcs and delayed DNA repair. Consequently, sensitivity to radiotherapy was enhanced (*49*). Since EGFR overexpression in solid tumors is associated with poor prognosis and radiotherapy resistance (*49, 51*), the miR-7 axis may represent a novel approach to improve radioresponse.

However, other miRNAs appear to act predominantly by different repair pathways of non-DSB DNA damage or other DNA repair mechanisms. In radiation-resistant esophageal adenocarcinoma cells overexpression of miR-31 has been shown to contribute to re-sensitization towards radiation and altered expression of 13 DNA repair genes (*45*). Interestingly, most of the altered genes are involved in

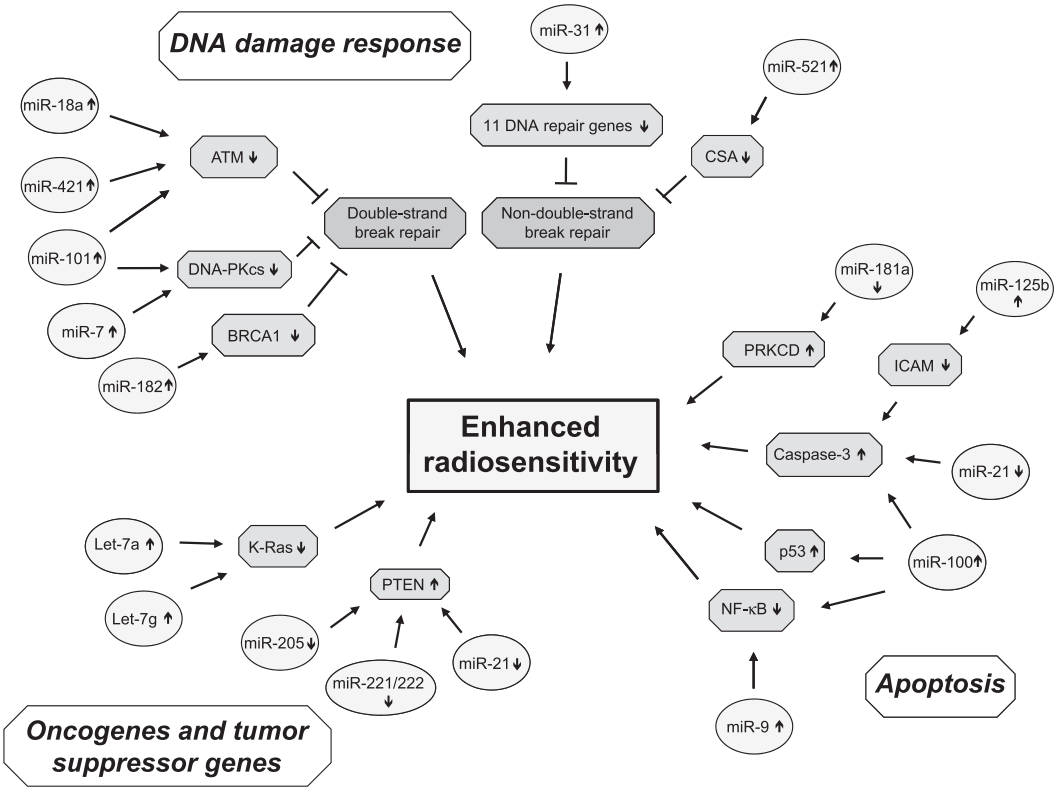

FIG. 1. Impact of miRNAs and targets relevant to radiation response.

base excision repair, mismatch repair and nucleotide excision repair pathways, which do not primarily belong to DSB repair machinery. This is surprising, given that previously published data from the authors of this study showed enhanced DSB repair in the same radiation-resistant cells (*45, 52*). However, the authors hypothesized that different DNA repair pathways are critically interlinked (*45*). In addition, overexpression of miR-521 sensitized cells to radiation, while inhibition of miR-521 resulted in radioresistance. Radiation treatment, as well as downregulation of miR-521, led to increased levels in the DNA repair protein, Cockayne syndrome protein A (CSA), one of the predicted target genes of miR-521 (*37*). Low levels of miR-200c have been shown to correlate with radioresistance in breast cancer cells, and overexpression of miR-200c enhanced radiosensitivity mediated by enhanced radiation-induced DSBs/apoptosis rates as well as decreased proliferation rates with TANK-binding kinase 1 (TBK1), a possible target of miR-200c (*53*).

MiRNAs Regulating Relevant Cellular Signaling Pathways

In addition to DNA damage response by DSB repair machinery or non-DSB DNA damage repair mechanisms, other cell-signaling pathways can impact the cellular response to radiotherapy. For example, oncogenes and tumor suppressor genes (*54*) or apoptotic genes (*55*) can affect radiosensitivity. miRNAs play a crucial role in the regulation of these signaling pathways, as summarized below.

Oncogenes and tumor suppressor genes. One well-known tumor suppressor gene is PTEN (phosphatase and tensin homolog), which acts by negatively regulating the PKB (protein kinase B, Akt) signaling pathway. This mechanism is critical for the regulation of the cell cycle, cell growth and apoptosis (*54, 56*). In recent years, several authors have identified numerous miRNAs that can interfere with the PTEN pathway. For instance, PTEN has been proven to be a target of miR-221/-222. Knockout of these miRNAs results in increased PTEN levels, which in turn lead to suppressed Akt activity and increased apoptosis, and most importantly, to enhanced radiosensitivity in various cancer cell lines (*57*). These results are in agreement with observations by other authors reporting studies using gastric (*58*) and colorectal cancer cell lines (*54*). Furthermore, PTEN is a known target of miR-21. Mimics of miR-21 inhibited PTEN expression and enhanced radioresistance in non-small cell lung cancer cells (*59*), and inhibition of miR-21 increased radiosensitivity via PTEN in esophageal cancer (*60*). An additional miRNA that potentially targets PTEN is miR-205. Qu *et al*. demonstrated that miR-205 increased radioresistance of nasopharyngeal carcinoma, potentially by directly targeting PTEN (*24*).

Another relevant oncogene that is directly regulated by miRNAs is K-RAS. In the context of radiotherapy resistance, the lin28-let-7 axis might be of relevance (*61*). Ras proteins act as proto-oncogenes, and their 3′UTRs contain let-7 complementary sites, which enable let-7 to act as a tumor suppressor to regulate Ras expression (*31*). Activation of Ras signaling has been shown to increase survival of tumor cells exposed to radiation (*62*). Recently, this regulatory network was analyzed in two studies, and overexpression of let-7a was shown to suppress K-Ras expression, which in turn radiosensitized lung carcinoma cells (*61*). In line with these results, enhanced radiosensitivity was also achieved by inhibition of lin28, a repressor of let-7, and this was also followed by decreased K-Ras expression (*61*). Similar findings have been observed for let-7g (*63*).

Apoptosis. The cellular response to radiation is related to cell cycle and apoptosis, and a number of miRNAs play key roles in radiation-induced apoptosis (*55*). For example, miR-21 seems to be linked to the apoptotic pathway in lung cancer cells, and miR-21 contributes to radioresistance by blocking the pro-apoptotic gene caspase-3. Downregulation of miR-21 leads to increased radiosensitivity, possibly by inhibition of cell cycle progress and proliferation (*64*). Another miRNA that impacts radioresistance by apoptotic pathways, miR-125b, appears to be a potential regulator of intercellular adhesion molecule-2 (ICAM-2), which has been linked to radiosensitivity in oral squamous cell carcinoma by interaction with apoptotic signaling pathways (Akt and caspase-3) (*65*). Overexpression of miR-125b results in decreased ICAM-2 levels and proliferation rates (*66*). Induction of apoptosis, possibly mediated by inactivation of the PI3K-Akt pathway, can also be a result of miR-126 overexpression, and lead to enhanced radiosensitivity (*22*). In an irradiated non-Hodgkin's lymphoma cell line, miR-148b has been found to increase radiosensitivity of cells (*67*). In this context, radiation-induced apoptosis through repression of DNA methyltransferase 3b (DNMT3b) is a possible underlying mechanism (*67*). In addition, miR-181a targets another pro-apoptotic gene, PRKCD (protein kinase C delta type) and contributes to radioresistance by negative regulation of PRKCD expression and inhibition of radiation-induced apoptosis in cervical cancer cell lines (*12*). Furthermore, miR-196a overexpression has been shown to increase proliferation rates and radioresistance in head and neck tumors (*25*). An important component in the signaling pathway is the tumor suppressor annexin A1 (ANXA1), which is a target gene modulated by miR-196a. Interestingly, miR-196a overexpression and ANXA1 knockdown result in similar oncogenic phenotypes (*25*). Finally, miR-100 has recently been shown to modulate expression of apoptotic genes as well. In a colorectal cancer cell line, expression of p53 and caspase-3 (both pro-apoptotic) was increased by miR-100, while the expression of Bcl-2 and NF-κB (both anti-apoptotic) was decreased. Upregulation of miR-100 therefore sensitized cells to radiation (*55*). In addition to involvement in numerous important processes such as immune and inflammatory response, the transcription factor NF-κB is

also known as crucial early response gene responsible for modulating cellular response and apoptosis in response to injury (*68*). Interestingly, the activated NF-κB pathway is linked to radioresistance, and suppression of this pathway might offer another opportunity to overcome radioresistance (*69*). Expression of miR-9 has been show to correlate negatively with NF-κB expression in irradiated lung cancer cells and overexpression of miR-9 results in decreased NF-κB levels, leading in turn to increased sensitivity towards radiotherapy (*70*). Similar effects have been demonstrated for let-7g, suggesting that both miRNAs regulate response to radiation through inhibition of NF-κB (*70*).

CONCLUSION

Recently reported research provides limited but promising data pertinent to miRNAs and their impact on radiotherapy for cancer. miRNAs offer potential as new biomarkers to inform decisions in a clinical setting. miRNAs might be used not only to predict and monitor radiotherapy responses, but to modulate radiotherapy response as well. Mechanisms of action by which miRNAs affect radiation sensitivity include modulation of DNA damage response and regulation of cellular signaling pathways such as oncogene, tumor suppressor genes or apoptosis. miRNAs hold significant potential as diagnostic, prognostic and therapeutic targets for use in the near future. More studies are needed to further demonstrate the potential expanded role of radiotherapy in targeted molecular-based diagnostics and cancer treatment.

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