Perspective

MicroRNAs as novel elements in personalized radiotherapy

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Abstract: Radiotherapy (RT) is a widely used and effective non-surgical cancer treatment. However, the mechanism behind several major challenges to efficacy, such as tumor radioresistance, normal tissue toxicity, individual radiation hypersensitivity and promoted metastatic spread, are not fully understood. The involvement of microRNAs (miRNAs) in processes important for tissue radiation responses, including DNA damage repair, activation of signalling cascades or changes to the microenvironment, is being recognized. Most recently, the exchange of miRNAs between irradiated and non-irradiated cells through microvesicles was described as a new component of the cellular radiation response. The therapeutic inhibition or mimicking of miRNAs to overcome radioresistance during therapy, and the usage of miRNAs as predictive biomarkers for therapy response and prognosis, are promising applications of miRNAs in RT. However, due to the lack of *in vivo* or clinical studies the full potential of miRNAs for RT is difficult to estimate. In summary this contribution gives an overview about new understanding of the miRNA involvement in the radiation response and summarizes first RT-related applications.

Keywords: MicroRNA (miRNA); ionizing radiation (IR); personalized therapy; biomarker; radiosensitizer

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Introduction

Radiotherapy (RT) is a widely used cancer treatment modality. Around 50–60% of all cancer patients undergo RT. Despite considerable progress, especially in technical developments, there are still challenges to be met. These include tumor radiation resistance and the killing of normal tissues which result in poor tumor control and/or severe side effects respectively (1,2). Both of these could be counteracted through the administration of agents that enhance tumor radiosensitivity. Ideally, such agents should also reduce the radiosensitivity of healthy tissue. A second major demand to promote and personalize RT in the future is the development of strategies for the prediction of clinical relevant RT parameters, such as tumor control and long-term side effects (3).

A promising class of molecules where targeting may be able to overcome these challenges are the family of microRNAs (miRNAs). These non-protein coding RNA molecules are already showing potential as biomarkers in many clinical situations, and are under development as therapeutics for the treatment of a variety of diseases. Some miRNAs have already reached clinical phase I and II trials (4). In the context of radiation, a wealth of data, mainly obtained from *in vitro* studies, describes radiosensitizing or radioprotective functions to individual miRNAs that respond during radiation response (5). First reports suggest an application for miRNA signatures as predictive biomarkers in both therapy responses and disease prognosis (see section miRNAs as biomarkers). Most interestingly, beside their established intracellular functions, miRNAs have been detected in body fluids where they may act as signal molecules coordinating cell-cell communication.

A new study describing miR-125b as a putative

sensitizer in RT (6) prompted us to discuss the most recent progress in understanding and application of miRNAs for radiosensitivity and RT.

miRNA basics

miRNA are small (~22 nucleotides) non-coding sequences transcribed from the genome under regulatory control. They are non-coding RNA molecules acting as regulators of gene expression (7,8). In general, they negatively regulate gene expression at the post-transcriptional level by preventing efficient translation of messenger RNA (mRNA) or by accelerating mRNA degradation. The miRNA-mediated regulation of cellular phenotype is characterized by a high complexity, because each miRNA is able to act upon several different target genes, whilst one target gene can be regulated by many different miRNAs (9,10). Computional calculations suggest a miRNA-mediated regulation on around 60% of all protein-coding genes. To control such widespread miRNA-mediated functions cells have evolved numerous sophisticated mechanisms to regulate miRNA abundance on the levels of transcription, maturation and stability (11).

miRNA biogenesis and maturation comprises of several steps of processing of a primary nuclear transcript (pri-miRNA) that may be mono- or multicistronic (11). After capping and polyadenylation the pri-miRNA is cleaved by the RNase III enzyme DROSHA into a precursor form (pre-miRNA) and exported into the cytoplasm. The pre-miRNA enters into a complex with a second RNase III enzyme, DICER, where it is processed into the mature form. Subsequently, the 19–23 nucleotide RNA duplex is transfered into the RNA-induced silencing protein complex (RISC). Here the double stranded miRNA is unwound to leave a single stranded miRNA species that is ready to bind a complimentary sequence in the target mRNAs as part of an RISC complex.

Functionally miRNA actions are implicated in the regulation of diverse cellular processes ranging from cellular homeostasis to stress responses (12). Moreover, they have been implicated in many diseases (13).

However, beside their intracellular functions, miRNAs are also present in the extracellular space. miRNAs can be robustly detected in body fluids like plasma, saliva or urine (14). This extracellular miRNA population is heterogeneous and variable. Some miRNAs are packaged into apoptotic bodies, shedding microvesicles, exosomes, or high density lipoprotein (HDL) particles, whereas others are solely complexed with AGO proteins (14). Comparison of miRNA expression profiles in donor cells and in vesicles showed significant differences, suggesting specific packing mechanisms for microvesicle cargo. Moreover the exosomal cargo composition can be altered in response to physiological and pathological conditions such as cellular stress or diseases (15). So far the functions of extracellular miRNAs are not entirely clear, but it was shown that extracellular microvesicle-embedded miRNAs can be transfered and incorporated into recipient cells (16). Most interestingly a recent report described the cell-independent maturation of miRNAs in exosomes from cancer cells (17).

miRNAs as regulators of radiation response

Ionizing radiation (IR) changes intracellular miRNA expression

The essential role of miRNAs in an effective cellular response to radiation exposure was discovered in at least two studies. Kraemer *et al.* showed in endothelial cells that RNAi downregulation of either of two essential processing enzymes, AGO2 or DICER, leads to a global suppression of miRNA levels, and in turn to an increased level of cell death after γ-irradiation. This indicates a prosurvival function of miRNAs in endothelial cells (18). In accord with this observation Surova *et al.*, found that the miRNA processing enzymes DROSHA and DICER were expressed at higher levels in radioresistant compared to sensitive cell lines (19). Many subsequent studies have shown that IR changes the expression of specific subsets or of individual miRNAs, that have an impact on radiosensitivity (5,20). For miR-21 it was even suggested that the extent of radiation-induced change in the miRNA itself is correlated with high or low cellular radiosensitivity (21). Overall, radiation-induced changes in miRNA expression are transient, dependent upon dose, and are cell type specific. Reports showing common patterns in radiation-triggered deregulation that extend across several cell types, as found for the let-7 family miRNAs or for miR-525-3p, are rare (5,22). For some miRNAs repression in their levels after exposure has been described. Although a mechanistic basis is not yet available reduced levels can be assumed to promote translation of specific miRNA target proteins. Mechanisms proposed to link a radiation response to increased miRNA biogenesis, however, include increased processing of pri-miRNAs through KSPR after phosphorylation by the DNA damage sensor protein ATM or the induction of pri-miRNA transcription by the DNA damage stabilized transcription factor p53 (e.g., miR-34 family) (23,24). Together these findings all hallmark miRNAs to potential key players in determining the

response to IR and, by inference, to RT.

miRNAs regulate intracellular radiation response processes

Functionally, miRNAs affect many aspects of tumor radiation sensitivity by regulating cellular key components in cell cycle arrest, DNA damage repair, cell death and radiation related signal transduction (25). On the one hand miRNAs can impair production of proteins essential for DNA damage recognition, signalling, and cell cycle arrest essential to initiate repair. This may lead to lower DNA repair capacity and radiosensitivity. For example miR-24 and miR-451 repress the DNA damage sensor proteins H2AX and ATM (26,27). Additionally, both miRNAs also affect cell cycle progession during stress response. miR-421 targeting of ATM impairs S-phase cell cycle arrest and miR-24 regulates the cell cycle proteins cyclin A and E as well as the retinoblastoma protein.

On the other hand the repair process itself may also be targeted by miRNA action. Examples are miR-210, which represses the RAD52 protein involved in homologous recombination or miR-101, which regulates the DNA-PK kinase essential for non-homologous endjoining (28,29). The subsequent steps in the radiation response, culminating in death or survival may also be influenced by miRNA-mediated regulation of signalling pathways, like PI3K/AKT, nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK) and transforming growth factor-beta (TGFβ). Thus, the suppressive effect of miR-221 and miR-222 on the AKT upstream tumor suppressor PTEN leading to increased cell death and radiosensitivity was studied in gastric carcinoma cells (30).

Extrinsic factors, such as local hypoxia and angiogenesis are also important determinants of tumor radiation resistance. Both are critical components that establish the tumor microenvironment and are not suprisingly also regulated by miRNAs. Of particular importance is the hypoxia accelerated miR-210, which enables tumor survival by impairing cell cycle checkpoint activation, homologous recombination and cell death regulation (28,31).

Vesicle-mediated miRNA communication in the radiation response

A completely new field has arisen since the discovery that extracellular miRNAs are potential tools for cell-cell communication during radiation response. In radiation responses of complex tissues the existence of non-targeted effects (bystander or apscopal effects) in cells or tissues that have not been in direct contact with irradiation is well documented. Here again, the underlying mechanisms are not entirely clear (32).

Several recent studies now suggest that microvesicles, especially exosomes and their miRNA cargo, may be able to act as mediators of non-targeted effects. A possible functional link between microvesicles and the radiation response is supported by the finding that p53, upregulated by stabilization during radiation response is also essential for exosome biogenesis (33). In line with this finding Arscott *et al*. reported a more pronounced increase in radiation-induced exosome release for p53-proficient glioma cells compared to p53-deficient cells (34). Elevated exosome release after irradiation was also reported for human keratinocytes HaCAT (35), breast epithelial tumor cells MCF7 (36), human prostate cell lines (37) and for the head and neck cancer cell line BHY (38). In head and neck as well as glioma cells an increased release of exosomes is accompanied by the increased exosome uptake in irradiated cells. Mechanistically these findings may be explained by a recent study of Hazawa *et al*., which showed that radiation induces the colocalization of CD29 and CD81 onto the surface of mesenchymal stem cells, where exosomes engage them and are specifically captured (39).

As miRNA changes within microvesicles are reported for other stressors it appears likely that IR will also be able to selectively change the vesicle cargo (40). So far this was only evident in a few studies. One study performed miRNA profiling in exosomes derived from glioblastoma cells and detected a considerable number of up- and downregulated miRNA within the exosomes after irradiation of the donor cells (34). Tang *et al*. reported increased exosome amounts, together with changes in the expression of four miRNAs in the serum of lung cancer patients after irradiation (41). After *in vivo* irradiation of rats Beninson *et al*. showed decreasing miR-142-5p and miR-203 within circulating exosomes, which are associated with immunomodulatory functions (42). Xu *et al*. showed the participation of exosomal miR-21 in radiation induced bystander effect. He demonstrated that exosomes isolated from irradiated conditioned medium could induce bystander effects by mediating miR-21 transfer from irradiated to bystander cells. Inhibition of miR-21 before irradiation abrogated these effects (43). Nonetheless bystander effects can also be triggered by miRNA transfer without extracellular vesicles. In this context Yuan *et al*. showed that the extracellular radiation-increased miR-1246 can act as a cell-to-cell messenger which induces radioresistance by targeting the DR5 mRNA in recipient

cells independent of extracellular vesicles (44).

miRNAs for clinical applications in RT

miRNAs may have future applications as diagnostic and therapeutic tools in RT. Current data on clinical miRNA applications are mainly reports on circulating or tissue biopsy-localized miRNAs as biomarkers for therapy response and prognosis. Nonetheless, the application of miRNAs as radiosensitizers during RT is being increasingly recognized.

miRNAs as biomarkers

The potential of miRNAs as biomarkers lies in their (I) specificity for the administered treatment; (II) stability in tissues, together with their stable release into body fluids (e.g., blood or urine); (III) fast, robust and economic detection of miRNA expression signatures [even after long-term storage or formalin-fixed parafine embedding (FFPE)] (45).

First studies have reported radiation-induced miRNA changes within tumor tissues which may be used as RT biomarkers. Drebber *et al*. showed that low intratumoral miR-145 expression post chemo-RT correlated with poor neoadjuvant chemo-RT-response in rectal cancer patients (46). Expression profiling of postoperative RT-resistant and -sensitive non-small cell lung cancer patient samples revealed 12 deregulated miRNAs samples in which the radioresistent cases were correlated with low miR-126 and miR-7a expression (47). Few reports so far suggest the potential use of miRNAs in predicting/quantifying RT-related normal tissue toxicity. Talwar *et al*. demonstrated in a mouse model that miRNAs can affect mRNA regulation and apoptosis during oral mucositis (48). In another study a potential role of miR-210 in regulating radiation-induced intestinal fibrosis was shown (49).

Accordingly, several reports suggest plasma miRNA expression as novel biomarkers to predict RT response in a clinical context. The analysis of circulating miRNA levels in blood samples of breast cancer patients before and after RT demonstrated that miR-21 and miR-206 were up-regulated while miR-7, -34a, -29, -15 and -16 were down-regulated in radioresistant patients (50). A study in esophageal squamous cell carcinoma patients identified that the plasma miR-16 expression level has considerable clinical value in predicting RT outcomes (51). In line with these findings Summerer *et al*. identified patient-specific and therapy-responsive miRNAs in the plasma of head and neck cancer patients. High expression of miR-142-3p, miR-186-5p, miR-195-5p, miR-374b-5p and miR-574-3p correlated with poor prognosis (52,53).

Therapeutic applications of miRNAs

miRNAs may also be used as radiosensitizers in RT in the future. *In vitro* studies suggest a number of candidate miRNAs whose manipulation leads to radiosenzitation. Recently it has been recognized that therapeutic inhibition of miRNAs or mimicking of miRNAs may be a useful tool for overcoming radioresistance during therapy. The usage of miRNAs in therapeutics is attractive as the miRNA effect is tuning of target expression instead of knocking it out which should be less detrimental to healthy tissues. Moreover, as miRNAs can simultaneously target many genes within a pathway or even multiple pathways therapy resistance may be reduced compared to radiosensitizers developed against one target.

New technologies for the silencing of miRNA functions like antimiRs, locked nucleic acid (LNA) antisense oligonucleotides and miRNA sponges, which act as competitors for miRNA-target interactions are now ready to test their application *in vivo*. Examples are two recent studies showing the treatment of hepatitis C virus infections. One report showed the treatment of chronically infected chimpanzees with a LNA-modified oligonucleotide complementary to miR-122 which leads to the suppression of hepatitis C virus viremia (54). Another study demonstrated an antimiR treatment for chronic hepatitis C viral infection in humans in a phase II clinical trial (55). Moreover, there are also approaches to mimic or overexpress miRNAs, for example by using lipid-formulated mimics and adeno-associated virus vectors. One group treated lung cancer xenografts using liposomal nanoparticles loaded with miR-200c mimics, and showed that this sensitized tumours to irradiation by regulating the cell oxidative stress response (56).

To facilitate miRNA applications in RT systems the selective delivery to target cells in effective concentrations is necessary. A new approach to overcome this issue is the usage of engineered viral particles for cell transduction with miRNA overexpressing or inhibiting vector constructs (57).

Challenges for miRNA applications in RT

Available data have demonstrated that miRNA expression is a key component in cellular radiosensitivity and *Figure 1*

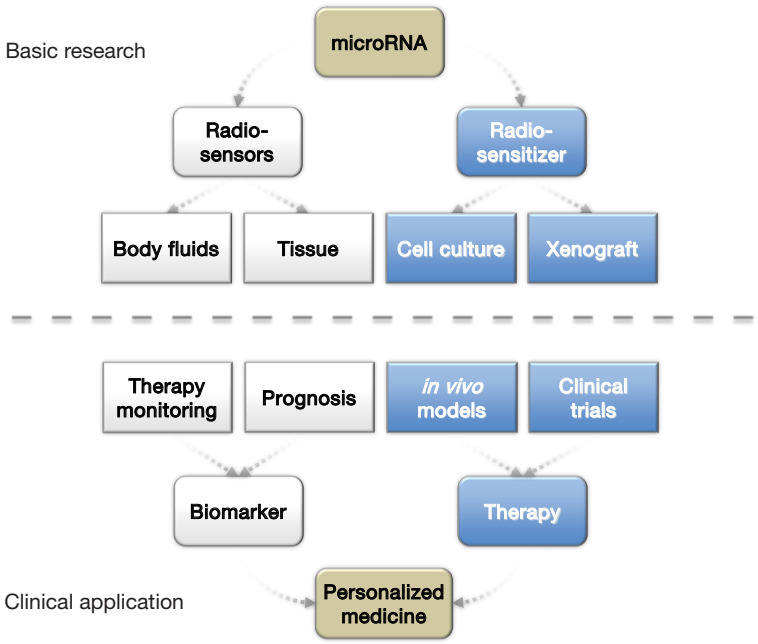

Figure 1 Summarizing scheme of translational microRNA (miRNA) research. The aim of the basic miRNA research is to provide the experimental basis for future clinical applications by finding radiosensors and modulators of radiosensitivity. This strategy aims at facilitating the evaluation of miRNA applications as biomarkers and new therapeutic tools which contribute both to a personalized medicine approach.

summarizes how basic research and clinical miRNA applications may contribute to personalized medicine in future. Early data suggest that it may be possible to use tissue-derived and circulating miRNAs to predict patient response to RT. However further validations, especially prospective trials, are required to establish the usefulness of miRNAs as biomarkers in RT. For example although quantification techniques have high sensitivity and specificity no consensus has been reached regarding best normalization protocols, standardized sample preparation or choice of body fluid (e.g., plasma/serum). Additionally, the small numbers of samples studied may hide bias due to individual sensitivities, concurrent chemotherapies and even assay protocols at all demand independent validation studies.

Current data also challenge the applicability of miRNA targeting for radiosenzitation. With few exceptions, even strong changes in the miRNA content by overexpression or miRNA inhibition only induce small changes in radiation sensitivity. This may be consistent with their biological function as fine-tuners of expression; however, it remains to be investigated if such limited effects are sufficient for putative clinical applications. Regarding limited effect sizes the investigation of cooperative effects resulting from the simultaneous manipulation of several miRNAs may be helpful. Moreover, there is insufficient knowledge about miRNA functions in more clinically relevant experimental scenarios such as dose fractionation/hyperfractionation, use of different radiation qualities (protons, carbon ions) or prevailing hypoxic conditions. Most importantly there is a lack of knowledge about the transferability of *in vitro* or xenograft data of candidates into *in vivo* models or patient materials.

Conclusions

In conclusion, research performed thus far supports a relevant role for miRNAs in the future of radiation oncology, which may provide the basis to predict response of RT patients and to develop miRNA-based customized treatments to enhance radiosensitivity. Early studies showed that the usage of miRNAs as biomarker for therapy monitoring and prognosis and therefore for more precise and personalized treatment of patients, is possible. Treatment applications for miRNAs as radiosensitizer are currently restricted to cell culture or xenograft model

systems and need to be transferred into *in vivo* in the future.

Currently least understood is the function of extracellular miRNAs. A detailed investigation of radiation triggered mechanisms for secretion, transfer and function in recipient cells may contribute to the understanding of important RT issues such as apscopal effects or radiation induced secondary tumors.

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Footnote

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