Published in final edited form as:

Curr Opin Genet Dev. 2018 February ; 48: 128–133. doi:10.1016/j.gde.2018.01.001.

Emerging roles of microRNAs in cancer

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Abstract

MicroRNAs (miRNAs) have emerged as important regulators of human carcinogenesis by affecting the expression of key oncogenes and tumor suppressor genes. MiRNAs elicit their function through post-transcriptional regulation of the mRNA translation into protein as well as functioning as ligands for proteic receptors called miRceptors. Our understanding of the role of miRNAs in cancer biology has enormously improved in the last few years, providing the rationale for new therapeutics. Here we discuss the most recent findings on the role of miRNAs in modulating cancer biology with a specific focus on their role of modulators of the biology of the Tumor Microenvironment both as cargo of extracellular vesicles and as extra-vesicular miRNAs.

Keywords

miRNAs; cancer; extracellular vesicles

Introduction

Cancer is a leading cause of death worldwide. In the last three decades, researchers have identified new cancer-specific targets that have allowed to develop anti-cancer target therapies with an important reduction of side effects. Clonal evolution of cancer cells leads

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Authors' contributions

All the authors were involved in drafting the manuscript, revising it for intellectual content, and reading and approving the final manuscript.

Competing interests

The authors declare that they have no competing interests.

to a variety of survival pathways allowing cancer cells to survive and become resistant to current treatments. Small molecules have been discovered to affect the signal transduction pathways for the survival and proliferation of cancer cells [1]. Among these, microRNAs (miRNAs) are important modifiers of transcription and translation of key regulatory proteins involved in cancer development and progression. They can inhibit or enhance the expression of oncogenes or tumor suppressor genes, therefore profoundly affecting the biology of cancer. MiRNAs belong to a large and growing family of small non-coding RNAs. They have a nucleotide sequence of 19–24 bases in length and they control gene expression by targeting specific mRNAs usually at the level of the 3′ untranslated region (3′-UTR) of the transcript, albeit other less conventional targeting sequences have been identified. A specific mRNA may be targeted by different miRNAs and a single miRNA can have several mRNA targets. MiRNAs are involved in the communication between cancer cells and the surrounding tumor microenvironment (TME). The interaction between tumor cells and components of TME may directly influence all aspects of cancer biology. Extracellular vesicles (EVs) are mediators of the inter-cellular cross-communication occurring within the TME [2, 3]. EVs are characterized by a lipidic bilayer membrane analogue to the plasma membrane and a size ranging from 30 nm to a few microns. EVs are classified into three categories based on their size: exosomes with a size of 30-100 nm, microvesicles with a size ranging from 100 to 1000 nm, and large oncosomes with a size ranging 1-10 μm. Furthermore, all EVs carry a complex cargo composed of proteins, mRNAs, DNA, short and long non-coding RNAs such as miRNAs that can influence the cancer growth. Exosomal miRNAs contribute to angiogenesis by modulating the expression of pro- and anti-angiogenic factors. In this review, we will focus on the most important miRNAs dysregulated in tumor cells and their molecular mechanisms to regulate the expression of target genes involved in cancer growth. Finally, we will discuss the key role of miRNAs in the communication between the TME and tumor cells through EVs.

miRNAs expression regulations

miRNAs are dysregulated through different mechanisms. One of these was described by Nawaz *et al.*. They discovered that the *miR-4484* is a downregulated tumor suppressor in glioblastoma and it located on chromosome 10 at fragile loci that undergoes a somatic copy number alteration through a deletion of miRNA sequence [4]. Zhou *et al.* showed that the amplification of the gene encoding for *miR-30d* promotes cervical carcinoma growth and progression [5].

Furthermore Yin *et al.* demonstrated that *miR-33b* is a tumor suppressor and the CpG island hypermethylation upstream of *miR-33b* determines its downregulation in gastric cancer [6].

miRNAs as oncogenes or tumor suppressor genes

MiRNAs are often dysregulated in cancer patients compared to the normal tissue counterpart. The predicted targets of these miRNAs include both oncogenes and tumor suppressor genes. *MiR-155* is upregulated in many human cancers and in more aggressive and therapy-resistant cancers as Van Roosbroeck *et al.* demonstrated [7]. The authors of this study observed that downregulation of *miR-155* achieved through a treatment with *anti-*

miR-155 successfully re-sensitized tumors to chemotherapy in an *in vivo* orthotopic lung cancer model. Moreover, they observed a negative feedback loop between *miR-155* and *TP53* in 956 patients with lung cancer, acute lymphoblastic leukemia and chronic lymphocytic leukemia and showed that a signature of high levels of *miR-155* and low levels of *TP53* is significantly correlated with shorter survival in lung cancer.

Also *miR-9* is frequently upregulated in several human cancers [8, 9]. The study by *D'Ippolito et al.* showed that in triple-negative breast cancer, the most aggressive and undifferentiated subtype of breast cancer, *miR-9* has a high expression [10]. They observed that PDGFR β , a tyrosine kinase receptor for members of the platelet-derived growth factor family, induced *miR-9* expression, suggesting that *miR-9* behaves as a downstream effector of the receptor signaling. The authors discovered that *miR-9* targeted *STARD13*, a protein involved in the regulation of cytoskeletal reorganization, cell proliferation, and cell motility.

Bonci et al. dissected the role of *miR-15*, *miR-16* and *miR-21* in prostate cancer patients [11]. *miR-15* and *miR-16* are often downregulated in different tumors while *miR-21* is upregulated [12–14]. The authors of this study observed that the concomitant loss of *miR-15/miR-16* and gain of *miR-21* aberrantly activate the TGF- β signaling, increasing local invasion, distant bone marrow colonization and osteolysis by prostate cancer cells. In particular, they reported that *miR-15/miR-16* directly silences *USP9X*, an enzyme conducive of TGF- β signaling activation through the deubiquitination of *SMAD4*, whereas *miR-21* the TGF- β signaling inhibitor *SMAD7*. This study establishes a new molecular circuitry for prostate cancer that involves miRNAs.

Other miRNAs with tumor suppressor function belong to the *let-7* family. *Spolverini et al.* recently discovered that *let-7b* and *let-7c* can positively regulate the cellular expression of histone H2B (H2Bub1) in different type of tumors [15]. H2Bub1 influences chromatin function in transcription regulation and DNA repair. Cancer cells often show low levels of H2Bub1, and this promotes cancer progression. This positive regulation by *let-7b* and *let-7c* is achieved through the targeting of multiple mRNAs of the H2B deubiquitination machinery. In particular, *let-7b* and *let-7c* bind directly to and inhibit the mRNAs encoding for *USP42* and *USP44*, two components of the multiple deubiquitinating enzymes (DUBs). Furthermore, these miRNAs can silence the mRNA encoding for the adapter protein *ATXN7L3*, which is part of the DUBs complex.

Altogether, these data suggest that miRNAs can work both as oncogenes and as tumor suppressor genes both through a direct interaction with the regulated genes and through an indirect modulation of the epigenetic regulatory systems within the cell.

Oncogenic and tumor suppressor miRNAs discussed in this paragraph are summarized in Table 1.

Vesicular miRNAs in Cancer

Recently, EVs have emerged as a prominent way of communication between cells of TME, and they are currently also accepted as mediators of carcinogenesis [16]. Interestingly, EVs from cancer cells show a specific molecular profile both in terms of content and surface

markers, allowing their differentiation from EVs released by normal cells [17, 18]. Since Valadi *et al.* first demonstrated that miRNAs and other genetic material could be transferred from one cell to another by EVs, miRNAs have emerged as critical players in mediating all the processes that take place in the TME [19]. To date, very little is known about the main mechanisms of action through which vesicular miRNA elicit their functions in the recipient cells. Currently demonstrated mechanisms include the “classic” gene regulation operating through the miRNA binding to the 3′-UTR region of target mRNAs, and their “alternative” function mediated by the activation of miReceptors, defined as receptors for miRNAs. Yang *et al.* gave the first evidence of oncogenic miRNA transferring from macrophages to breast cancer cells *via* exosomes providing the rationale for the targeting of *miR-223* in M2 macrophages, or exosomal *miR-223* from M2 macrophages as therapeutics. By using a co-culture system they demonstrated that *miR-223* is shuttled from macrophages to breast cancer cells where it targets Mef2c and increases their invasiveness [20]. In the 4T1 murine breast cancer cell line, epigallocatechin gallate (EGCG), a molecule known for its anti-tumor effects, is able to suppress tumor growth. EGCG exerts its activity through the regulation of tumor-associated macrophages (TAM) in the TME, by up-regulating *miR-16* in tumor cells that is subsequently transferred to TAM *via* exosomes. *Ex vivo* incubation of TAMs with EGCG-treated 4T1 exosomes led to the increase of IL-6 and TGF-β, decrease of TNF-α, IκB kinase α (IKKα) suppression and concomitant IκB increase [21]. Oncogenic *miR-135b* was significantly upregulated in exosomes from a hypoxia-resistant multiple myeloma (HR-MM) cell model. Exosomal *miR-135b* from HR-MM cells downregulated its target factor—inhibiting hypoxia-inducible factor 1 (FIH-1) in endothelial cells, by targeting its 3′-UTR, enhancing endothelial tube formation under hypoxic condition, providing a possible target for controlling MM angiogenesis [22]. Recently, Patel *et al.* observed how conditioned media (CM) from pancreatic cancer cells treated with gemcitabine (Gem-CM) gave significant chemoprotection to later gemcitabine toxicity and provided clear evidence that the majority of the chemoresistance derived from the EV fraction of Gem-CM cells. Gene expression analyses demonstrated downregulation of Deoxycytidine kinase (DCK), a gemcitabine-metabolising gene, which is directly targeted by exosome-delivered *miR-155*, as confirmed by dual-luciferase 3′-UTR reporter assay [23]. Intriguingly, a recent study provided the first evidence about a cell-autonomous ability to process precursor miRNAs (pre-miRNAs) into mature form, describing how exosomes from breast cancer may transport pre-miRNAs complexed with Dicer, TRBP and AGO2 proteins [24]. Endovesicular miRNAs have been proven to function also by interacting directly with miReceptors. Fabbri *et al.* first identified a new mechanism of cell-to-cell communication demonstrating that exosomal *miR-21* and *miR-29a* from non-small cell lung cancer (NSCLC) cells, were recruited in the TME by TAMs and bind to their Toll-like receptor 8 (TLR8), activating the downstream NF-κB pathway, and increasing the secretion of interleukin-6 (IL-6) and Tumor necrosis factor α (TNF-α) which, in turn, promote an inflammatory TME conducive to increased cancer growth and dissemination [25]. In neuroblastoma, cisplatin resistance was increased by a *miR-155* mediated downregulation of Telomeric Repeat Binding Factor 1 (TERF1), a telomerase inhibitor. The underlying mechanism is a loop in which endovesicular *miR-21* from neuroblastoma cells, after its binding to TLR8 in surrounding TAMs, up-regulates *miR-155* which is then secreted in TAM-derived EVs, and transferred back to neuroblastoma cells where it silences TERF1 and increases resistance to chemotherapy [26].

The vesicular miRNAs mechanisms described in this paragraph are shown in Figure 1, whereas the vesicular miRNAs discussed in this article are summarized in Table 2.

Extra-Vesicular miRNAs in Cancer

It was previously demonstrated that miRNAs circulate in plasma and serum in a highly stable cell-free form, with a profile that can be altered in cancer and other diseases [27–29]. The high concentration of RNase activity in the bloodstream has prompted the scientific community to try to explain the mechanism underlying the surprising stability of circulating miRNAs (c-miRNAs). Initially, the release of c-miRNAs in membrane-bound vesicles (exosomes and microvesicles) with protective function was considered the most common form in which miRNAs were found in circulation. Surprisingly, this assumption was challenged by Wang *et al.* who found that biggest fraction of extracellular miRNAs was actually located outside of EVs [30]. Several studies have further supported this discovery. In 2011, Arroyo *et al.* showed that endovesicular miRNAs represent only a minor fraction of c-miRNAs, and that unexpectedly the majority of them co-fractionated with protein complexes, rather than with vesicles, protecting c-miRNAs from plasma RNases. These results significantly revised our knowledge about the physiological state and nature of c-miRNAs stability, with consequent backlashes on future studies about miRNAs as biomarkers and the function of extracellular miRNAs [31]. To date, less is known about the role and mechanism of action of Ago2/c-miRNA complexes, and it is also quite unclear whether they are released from viable cells and can be directed to recipient cells. C-miRNAs have also been found in association with lipoprotein such as low-density lipoprotein (LDL), or high-density lipoprotein (HDL) [32], which are able to carry nucleic acids and are often used as agents for gene delivery [33] (Figure 2). In patients with familial hypercholesterolemia, Vickers *et al.* identified for the first time a specific signature of miRNAs (including *miR-223*, *miR-105* and *miR-106a*) in HDL-miRNA complexes. Interestingly, the delivery of these HDL-miRNAs allowed a functional downregulation of their corresponding mRNA targets in cultured hepatocytes, suggesting the functional importance of these lipoprotein/c-miRNAs complexes [34]. In summary, while the full spectrum of mechanisms of action of c-miRNAs is still far from being elucidated, there is little doubt that they are involved in shaping the biology of cancer and of the TME.

Summary and Future Directions

MiRNAs regulate human carcinogenesis and affect the biology of the TME. They are also key mediators of inter-cellular communication both as c-miRNAs and as cargo of EVs. While the plethora of targets of frequently dys-regulated miRNAs has been the object of several studies, one of the biggest challenges is a better understanding of the selective mechanisms of secretion and delivery of extracellular miRNAs to the cells of the TME. Also, the specificity of uptake (if it exists) will improve our efforts of using miRNAs as therapeutics alone or, more likely, in combination with existing anti-cancer therapies. Finally, a broader study of the pattern of miReceptors and their topographic distribution within the cells of the TME will expand our understanding of this new fascinating branch of cancer biology and will extend our anti-cancer weaponry with the goal of increasing the number of saved lives of patients diagnosed with cancer.

Acknowledgments

Dr. Fabbri is a St. Baldrick Foundation's Scholar and is supported by the NIH/NCI grant R01CA215753, a Hyundai Hope on Wheels grant, a Jean Perkins Foundation grant, the Nautica Malibu Triathlon Funds, a STOP Cancer grant, the Hugh and Audy Lou Colvin Foundation grant, an Alex's Lemonade Stand Foundation grant, and the award number P30CA014089 from the National Cancer Institute.

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Figure 1. Mechanisms of action of Vesicular miRNAs

MiRNAs released by extra-cellular vesicles can interact with cells of the Tumor Microenvironment by binding to the 3'-UTR region of target mRNAs, or by binding to- and activating Toll-like Receptor 8 (TLR8) in surrounding cells of the immune system.

Figure 2. The fate of circulating miRNAs

MiRNAs can be released by cells in the surrounding microenvironment into three distinct forms: included in membrane-bound vesicles, associated with proteic complexes or in association with lipoproteins.

Table 1**Principal known**

miRNAs with Oncogene or Tumor suppressor role

miRNA	Tumor function	Cancer type	Target molecule	Author
miR-155	Oncogene	Lung cancer, Leukemia	TP53	[7]
miR-9	Oncogene	Breast cancer	STARD13	[10]
miR-21	Oncogene	Prostate cancer	SMAD7	[11]
miR-15	Tumor suppressor	Prostate cancer	USP9X	[11]
miR-16	Tumor suppressor	Prostate cancer	USP9X	[11]
let-7	Tumor suppressor	Lung cancer, Breast cancer	USP42, USP44, ATXN7L3	[15]

Table 2

Vesicular miRNAs involved in cancer

miRNA	Target Molecule	Involved Pathway	Involved Mechanism	Author
miR-223	Mef2c	Mef2c-b-catenin	3'UTR targeting	[20]
miR-16	IKK α	NF- κ B	3'UTR targeting	[21]
miR-135b	FIH-1	angiogenesis	3'UTR targeting	[22]
miR-155	DCK	acquired chemoresistance	3'UTR targeting	[23]
miR-21	NF- κ B	inflammation	TLR8 interaction	[25]
miR-29	NF- κ B	inflammation	TLR8 interaction	[25]
miR-21/miR-155	TERF1	Cisplatin resistance	TLR8 interaction	[26]