Review

Cancer Research

OncomiR or Tumor Suppressor? The Duplicity of MicroRNAs in Cancer

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Abstract

MicroRNAs (miRNA) are short, noncoding RNAs whose dysregulation has been implicated in most, if not all, cancers. They regulate gene expression by suppressing mRNA translation and reducing mRNA stability. To this end, there is a great deal of interest in modifying miRNA expression levels for the treatment of cancer. However, the literature is fraught with inconsistent accounts as to whether various miRNAs are oncogenic or tumor suppressive. In this review, we directly examine these inconsistencies and propose several mechanisms to explain them. These mechanisms include the possibility that specific miRNAs can simultaneously produce competing oncogenic and tumor suppressive effects by suppressing both tumor suppressive mRNAs and oncogenic mRNAs, respectively. In addition, miRNAs can modulate tumor-modifying extrinsic factors, such as cancer-immune system interactions, stromal cell interactions, oncoviruses, and sensitivity to therapy. Ultimately, it is the balance between these processes that determines whether a specific miRNA produces a net oncogenic or net tumor suppressive effect. A solid understanding of this phenomenon will likely prove valuable in evaluating miRNA targets for cancer therapy. *Cancer Res; 76(13); 3666–70. ©2016 AACR.*

Introduction

MicroRNAs (miRNA) are short, 18–25 nucleotide-long, noncoding RNA molecules that regulate gene expression by suppressing mRNA translation and reducing mRNA stability, usually through imperfect complementary base pairing to the 3′-untranslated region. Since their 1993 discovery in *C. elegans*, it has become ever more apparent that miRNAs are dysregulated in most, if not all, cancers. Many of these miRNAs either contribute to or repress the cancer phenotype by inhibiting the expression of tumor suppressors or oncogenes, respectively. Generally, oncogenic miRNAs (oncomiRs) are overexpressed in cancers while tumor-suppressive miRNAs are underexpressed. When these oncomiRs or tumor-suppressor miRNAs are inhibited or stimulated, respectively, cancer cell proliferation, metastasis, and/or survival may be significantly reduced, depending on the type of cancer and the specific miRNA being affected. It is even possible for cancers to become completely reliant upon, or "addicted", to an oncomiR, such that suppression of the oncomiR results in complete regression of the cancer (1). Thus, miRNAs have classically been categorized as either oncogenic or tumor suppressive, and controlling their expression for therapeutic purposes is the subject of intense ongoing research.

However, there is reason to propose that the therapeutic approaches should proceed with caution. The literature is fraught with conflicting reports as to whether specific miRNAs are oncogenic or tumor suppressive. Repeatedly, certain miRNAs have been shown to be oncogenic in one scenario, but tumor suppressive in another. Diversity of effects is not a surprise given the large number of genes influenced by a particular miRNA. It hence follows that the classification of a miRNA as oncogenic or tumor suppressive may represent an oversimplification that must be carefully scrutinized in all cancer miRNA studies. To date, this issue has received little consideration, and few studies have directly examined its potential causes.

Here, we highlight several examples in which a specific miRNA can act either as a tumor suppressor or an oncogene, depending on the context. We attempt to explain the phenomenon via examination of the affected cellular and molecular mechanisms, and we propose multiple factors that can influence whether a miRNA has a net oncogenic or net tumor suppressive effect. Finally, we argue for a holistic approach in examining the effects of miRNAs in cancer that incorporates the interactions of the miRNA's multiple targets and effects beyond the tumor cell, including interactions with the immune system, stromal cells, and therapy.

A Net Effect: The Targeting of Both Tumor Suppressors and Oncogenes

As an example of a miRNA that can act as either an oncomiR or a tumor suppressor depending on the context, we consider miR-125b. miR-125b acts as an oncomiR in the vast majority of hematologic malignancies but as a tumor suppressor in many solid tumors (2, 3). This apparent paradox can be reconciled by taking into account the fact that a single miRNA molecule has the capacity to target tens to hundreds of different mRNAs, some of which may have opposing oncogenic or tumor-suppressive functions. In the case of miR-125b, targets include mRNAs encoding antiapoptotic factors (MCL1, BCL2L2, and BCL2), proapoptotic factors (TP53, BAK1, BMF, BBC3, and MAPK14), proproliferative factors (JUN, STAT3, E2F3, IL6R, and ERBB2/3), metastasis promoters (MMP13, LIN28B, and ARID3B), metastasis inhibitors

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(STARD13, TP53INP1, and TP53), and factors involved in hematopoietic differentiation (CBFB, PRDM1, IRF4, IL2RB, and IL10RA; refs. 2, 3). Hence, it is likely that it is the balance of expression of these oncogenes/tumor suppressors that determines whether miR-125b will have a net oncogenic or net tumor-suppressive effect within an individual cancer. It is plausible that miR-125b largely exerts its oncogenic role in hematopoietic malignancies via the suppression of hematopoietic differentiation factors, which are of limited importance in most solid tumors. Combined with the suppression of miR-125b's other tumor-suppressive targets, the tumor-suppressive effects of miR-125b are trumped to produce a net oncogenic effect. For solid tumors, whether miR-125b is oncogenic or tumor suppressive is far more variable, likely because there is a more even balance between its oncogenic and tumor suppressive effects. Interestingly, the strong oncogenic role of miR-125b in hematologic malignancies can be overcome in certain instances. One notable example is chronic lymphocytic leukemia (CLL), in which miR-125b has been demonstrated to have a tumor-suppressive role (4). Although the possibility has not been directly investigated, one plausible explanation for this anomaly is that high overexpression of BCL2, an antiapoptotic target of miR-125b, is a critical hallmark of CLL (5). Thus, its suppression by miR-125b may be enough to tip the scales so that a net tumor-suppressive effect is produced.

Another excellent example of this phenomenon is provided by miR-155. By and large, miR-155 is considered an oncomiR. It possesses an oncogenic role in a large number of solid and hematologic malignancies (6–8), and its overexpression alone in lymphoid tissues is sufficient to produce an aggressive disseminated lymphoma in a miR-155 Cre-*loxP* tetracycline-controlled knock-in mouse model (6, 7). Consistent with miR-155's oncogenic potency, the lymphoma produced in these mice was demonstrated to be "addicted" to, or completely reliant upon, miR-155; tetracycline-induced withdrawal of miR-155 resulted in complete regression of the lymphoma (6). Nevertheless, despite its strong oncogenic effects, there is evidence that miR-155 has a tumor-suppressive role in some cancers. Levati and colleagues demonstrated that miR-155 inhibits proliferation in several melanoma cell lines, due in part to suppression of *SKI*, a commonly overexpressed oncogene in melanoma (9). Similarly, Li and colleagues and Qin and colleagues demonstrated that miR-155 exerts a tumor-suppressive effect in gastric cancer and ovarian cancer–initiating cells via targeting of *SMAD2* and *CLDN1*, respectively (10, 11). In addition, Palma and colleagues found that miR-155 has a proapoptotic and prodifferentiation role in *FLT3-wildtype* normal karyotype acute myeloid leukemia (NK-AML), which confirms that miR-155's tumor-suppressive role is not confined to solid malignancies (12). Strikingly, this was not the case for NK-AML harboring the *FLT3-ITD* mutation, which exhibited overexpression of miR-155 (12).

This set of observations highlights the variability of whether a miRNA is oncogenic or tumor suppressive, even within a single cancer type. Such variability is especially apparent when one considers that sequence variations are possible within the miRNA target sites of regulated genes. Multiple studies have shown that mutations and single-nucleotide polymorphisms can result in the functional loss of existing miRNA target sites (13, 14), as well as the creation of new miRNA target sites (15). Given the genetic heterogeneity of many tumors, it is hypothetically possible for a miRNA to exert opposing effects in different regions of an individual tumor, although examples of this have yet to be observed.

miRNA Interactions with Tumor-Modifying Extrinsic Factors: The Necessity of a Holistic Approach

The growth and spread of a cancer is not solely a function of the cancer cells themselves, but also of various extrinsic factors, which interact with the cancer cells to affect their behavior. Such factors include the immune system, tumor stromal cells, therapy, and oncoviruses. MiRNAs may have large influences on each of these factors, and it is hence necessary to maintain a holistic view when examining miRNAs from a therapeutic standpoint. This view should take into account all the aforementioned factors, not just the effects of the miRNA that are specific to the cancer cells themselves. Here, we present several examples of when a miRNA exerts an oncogenic effect on a tumor-modifying extrinsic factor but a tumor-suppressive effect on the cancer cells themselves, or vice versa (summarized in Fig. 1).

Contrasting effects on tumor-immune system interactions

miRNAs may modulate the interactions of cancer cells with the immune system. It is now well established that the interaction of immune cells with cancer cells in the tumor microenvironment can play an integral role in the growth and spread of the cancer. Both Zonari and colleagues and Yu and colleagues demonstrated that miR-155 deficiency in tumor-associated macrophages promotes conversion of the macrophages from the proinflammatory, antitumoral M1 phenotype to the anti-inflammatory, protumoral M2 phenotype (16, 17). Zonari and colleagues found that stable knockdown of miR-155 in the myeloid compartment of a mammary cancer mouse model resulted in increased tumor growth, and concluded that this was due to a decreased antitumoral immune response from tumor-associated macrophages (17). Similarly, Yu and colleagues observed that bone marrow transplantation from miR-155$^{-/-}$ mice to wild-type mice resulted in increased metastasis to the lung. They attributed this to M2 tumor–associated macrophage promotion of invasion and metastasis, as evidenced by an *in vitro* Transwell migration assay (16). In addition, an analogous role for miR-155 was found for tumor-associated dendritic cells in ovarian cancer. Cubillos-Ruiz and colleagues selectively delivered miR-155 precursor-containing nanoparticles to ovarian cancer–associated dendritic cells by taking advantage of the dendritic cells' spontaneous enhanced endocytic activity (18). This resulted in a transformation of the dendritic cells from an immunosuppressive phenotype to an immunostimulatory phenotype that triggered a potent antitumor immune response (18). Together, these studies clearly demonstrate the importance of considering miR-155's role in tumor-infiltrating immune cells when designing miR-155–based therapeutics. In the case where miR-155 suppression has a tumor-suppressive effect within the cancer cells themselves, it is likely that anti–miR-155 therapy would be optimized by targeting just the cancer cells and not the immune cells.

Two other examples of miRNAs that may have contrasting roles on tumor–immune system interactions and the cancer cells themselves are miR-30b and miR-30d. Both miRNAs target multiple oncogenes and are classified as tumor suppressors in the majority of studies that do not involve immune cells or

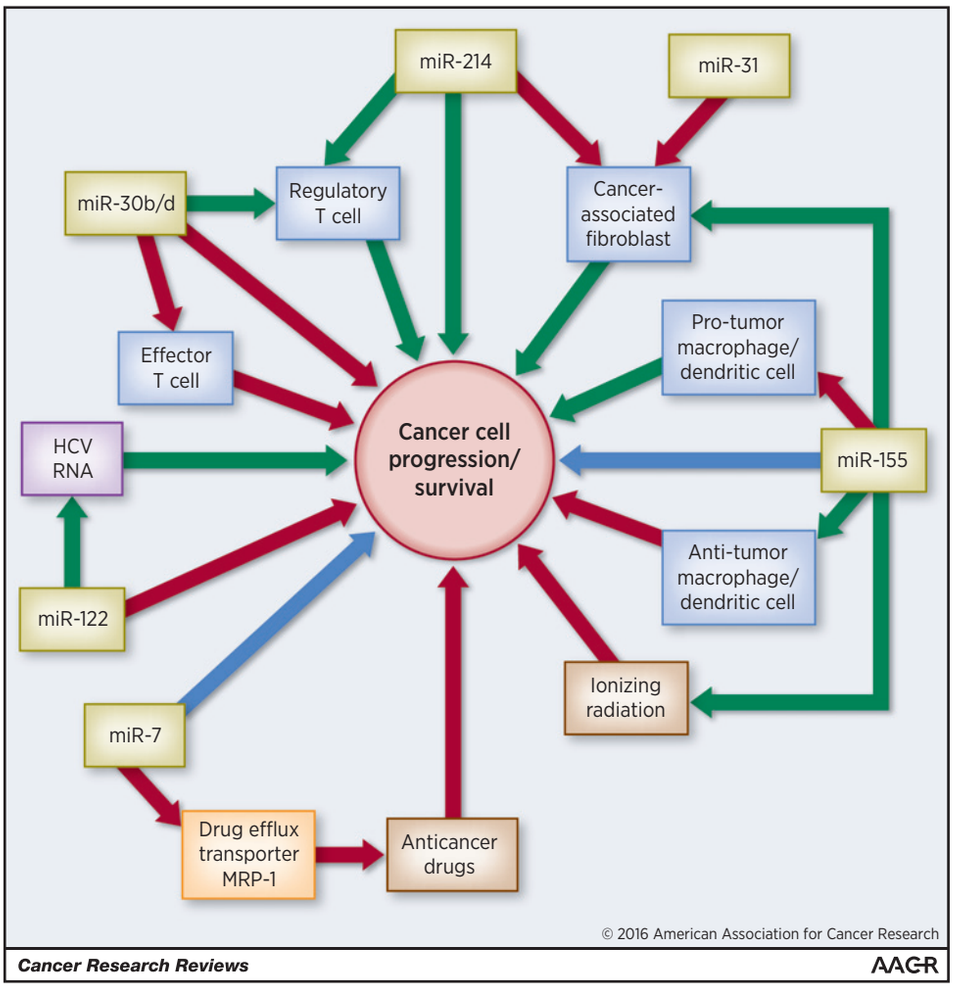

Figure 1.
Examples of miRNAs that may exert contrasting oncogenic/tumor-suppressive effects on tumor-modifying extrinsic factors and the cancer cells themselves. Green arrows, positive regulation; red arrows, negative regulation; blue arrows, either positive or negative regulation, depending on cancer cell type/context. An arrow extending directly from a miRNA to the central cancer cell refers to promotion/inhibition of cancer cell progression/survival through the miRNA's direct regulation of cancer cell–endogenous mRNAs.

immunocompetent mouse models (19, 20). However, Gaziel-Sovran and colleagues found that miR-30b/d promote secretion of the immunosuppressive cytokine IL10 by directly targeting the GalNAc transferase *GALNT7* (21). The increased IL10 from miR-30b/d-mediated *GALNT7* suppression resulted in reduced T-cell recruitment and enhanced regulatory T-cell induction within tumors in an immunocompetent mouse model for melanoma (21). This reduction in antitumor immunity was accompanied by a significantly increased number of metastases (21). Thus, examining a miRNA's effect on tumor–immune system interactions may be of the utmost importance when developing a miRNA-modulating therapy for cancer.

Contrasting effects on tumor stromal cells

miRNAs may also play a role in the interaction between cancer cells and non-immune cells of the tumor stroma, such as cancer-associated fibroblasts (CAF). It is now well established that non-immune cells of the tumor stroma can have a significant role in cancer progression. As a tumor develops, interactions between the cancer cells and the stromal cells may result in transformation of the stromal cells to a protumor state, which significantly enhances cancer growth, invasion, and metastasis. Although the mechanisms behind this transformation are poorly understood, they are partially elucidated by the discovery that miR-214 and miR-31 are consistently downregulated, while miR-155 is consistently upregulated, in ovarian cancer CAFs compared with normal fibroblasts (22). By triple-transfecting normal fibroblasts with miR-214 and miR-31 inhibitors and pre-miR-155, Mitra and colleagues were able to convert the fibroblasts to a CAF phenotype, which, like actual CAFs, significantly increased colony formation, migration, and invasion when cocultured with ovarian cancer cells *in vitro* and *in vivo* tumor growth when coinjected with ovarian cancer cells into mice. The reverse was also true; CAFs triple-transfected with miR-155 inhibitor, pre-miR-214, and pre-miR-31 exhibited a normal fibroblast phenotype (22). Notably, the cancer-promoting effects of the CAFs and the anti-miR-214/anti-miR-31/pre-miR-155 triple-transfected normal fibroblasts were largely mediated by increased expression of the cytokine CCL5, a direct target of miR-214, thereby supporting the notion that miR-214 acts as a potent tumor suppressor through the interactions of CAFs with ovarian cancer cells (22). Nevertheless, multiple studies attribute an oncogenic role to miR-214 (23, 24). Notably, one of these studies suggested miR-214 to be an oncomiR in ovarian cancer, the same type of cancer as in Mitra and colleagues' study, through the direct suppression of *TP53* (23). In addition, another of these studies demonstrated that miR-214 secreted within microvesicles by cancer cells can enter the bloodstream and exert an oncogenic effect through the induction of regulatory T cells, thereby suppressing the antitumor immune

response (24). Together, these results highlight the great complexity of this miRNA's role in cancer.

Location dependence of miRNA effects

Remarkably, the location of cancer cells can also govern whether a miRNA produces a net oncogenic or net tumor suppressive effect. This was demonstrated to be the case with miR-155 for 4T1 breast tumor cells injected into mice. Xiang and colleagues found that 4T1 cells virally transduced to overexpress miR-155 metastasized to a far lesser extent than control 4T1 cells after inoculation in the mammary fat pads of mice. Other factors, including tumor growth, remained the same. However, when the cells were injected directly into the blood stream, the miR-155–overexpressing cells produced far more metastatic lung tumors and increased tumor growth in the lungs compared with the control cells. Further analysis demonstrated that miR-155 inhibited epithelial-to-mesenchymal transition (EMT) in the cells by targeting *TCF4*, a key regulator of EMT. Thus, metastasis from the mammary fat pads was suppressed. However, at the same time, seeding and growth into the lung from cells that were already circulating in the bloodstream was increased, likely because the lung environment is more favorable for epithelial cell growth than it is for mesenchymal cell growth. It is possible that miR-155 overexpression promoted mesenchymal-to-epithelial transition (MET), a phenomenon many have proposed to aid the seeding of distant tissues by circulating tumor cells that have previously undergone EMT. Thus, miR-155 was tumor suppressive for 4T1 cells in the mammary fat pad but oncogenic for 4T1 cells in the blood stream and lungs. This holds important implications for the use of miRNA-modulating therapies to treat metastatic disease (25).

Contrasting effects on oncoviruses

Hepatitis C virus (HCV) infection results in the production of viral oncoproteins, chronic inflammation, and mutations in the liver that can ultimately lead to hepatocellular carcinoma. Thus, when treating a patient with hepatocellular carcinoma and concurrent HCV infection, it is important to consider a therapy's effect on not just the cancer cells, but also the HCV and immune system interactions. This may be the case with miR-122, a miRNA demonstrated to be tumor suppressive in hepatocellular carcinoma (26). Despite its antitumoral properties, miR-122 is also known to stabilize HCV RNA by binding to the 5′-untranslated region, thereby promoting HCV replication (27). In fact, Miraversen, a locked nucleic acid that inhibits miR-122 through antisense binding (27), is the most clinically advanced miRNA-targeting therapeutic in existence; it is currently in phase II clinical trials for the treatment of chronic HCV infection. Thus, treatment of hepatocellular carcinoma with exogenous miR-122 may actually enhance progression of the disease by promoting HCV replication. If a miR-122–promoting therapy is eventually developed for hepatocellular carcinoma, its use will likely require pre-screening for HCV infection. Interestingly, HCV RNA itself can be viewed as a miR-122 inhibitor by sequestering miR-122 from its host mRNA targets. Luna and colleagues demonstrated that HCV RNA functionally reduces the amount of miR-122 available for binding to its native targets, which could facilitate the oncogenic effects of HCV (28).

miRNA interactions with therapy

Interestingly, miRNAs may also affect the responsiveness to certain cancer therapies. Many studies that examine miRNA expression levels in cancer interpret a positive correlation between miRNA expression levels and increased survival as evidence that the miRNA is tumor suppressive. However, this kind of interpretation can be misleading. For instance, the miRNA may increase the proliferation of tumor cells but at the same time confer susceptibility to a treatment, resulting in increased overall survival. This was found to be the case with miR-155 in breast cancer patients treated with ionizing radiation (29). Ionizing radiation is a therapy that works by inducing double-stranded DNA breaks in cancer cells. These double-stranded breaks can be repaired via DNA homologous recombination, and thus upregulation of enzymes involved in this mechanism can confer resistance to the therapy. Gasparini and colleagues discovered that miR-155 directly suppresses the expression of RAD51, a protein critical for DNA homologous recombination, and thereby sensitizes triple-negative breast cancer to ionizing radiotherapy (29). As a result, patients with higher miR-155 levels, despite miR-155's oncogenic effects in this cancer (8), exhibited higher overall survival (29).

In addition, multiple miRNAs have been shown to suppress drug efflux transporters, and decreases in their levels are hence associated with chemoresistance (30). While the majority of these miRNAs seem to act consistently as tumor suppressors, this is not the case for miR-7, which has been described as both a tumor suppressor (31) and an oncomiR (32) for different cancer types. However, due to its suppression of the drug efflux transporter MRP1 (multidrug-resistance associated protein 1; ref. 33), miR-7 inhibition in cancers for which it is an oncomiR could produce an overall detrimental effect, as it could enhance chemoresistance, despite slowing the growth/spread of the tumor cells. Taken together, these results strongly argue for a holistic approach when investigating the exploitation of miRNAs as cancer therapy targets. Consideration must be given to the interactions of miRNAs with the immune system, tumor stromal cells, cancer therapies, and other factors extrinsic to the cancer cells themselves.

Conclusions

We have reviewed several of the mechanisms by which specific miRNAs can simultaneously exert competing oncogenic and tumor-suppressive effects. These effects extend from the regulation of various genes to the genes' downstream effects and to tumor-modifying extrinsic factors, such as immune system interactions and response to therapeutics. Depending on the balance between miRNA-mediated upregulation or downregulation of oncogenic and tumor-suppressive pathways, as well as the effects of the miRNA on cancer–immune system interactions and various other tumor-modifying extrinsic factors, the miRNA may produce an overall net oncogenic or net tumor-suppressive effect. A solid understanding of these mechanisms is of the utmost importance, as there is currently a great deal of excitement in the administration of exogenous miRNA mimetics and miRNA inhibitors for the control of various disease processes. This holds especially true for the field of cancer, as mounting evidence is suggesting that miRNAs are severely dysregulated in most, if not all, cancers. However, we suggest this endeavor be approached with caution, as it will likely require an excellent understanding of miRNAs from a holistic standpoint that incorporates all the aforementioned factors. To this end, we recommend the use of immunocompetent mouse models, which better replicate the tumor microenvironment, in preclinical studies of potential miRNA therapeutics. More studies investigating miRNA interactions with established

therapies would also be wise. Furthermore, due to the complexity of miRNA networks, systems biology approaches, which incorporate the interactions between various tumor-relevant systems at both the molecular and cellular scales, will be increasingly valuable. Such studies may prove necessary in order to fully utilize the vast clinical potential of miRNA therapeutics.

Disclosure of Potential Conflicts of Interest

F.J. Slack has ownership interest (including patents) in miRNA Therapeutics and Mira Dx and is a consultant/advisory board member for miRNA Therapeutics and miRagen Therapeutics. No potential conflicts of interest were disclosed by the other authors.

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