MiRNAs as Anti-Angiogenic Adjuvant Therapy in Cancer: Synopsis and Potential

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Angiogenesis is a key mechanism for tumor growth and metastasis and has been a therapeutic target for anti-cancer treatments. Intensive vascular growth is concomitant with the rapidly proliferating tumor cell population and tumor outgrowth. Current angiogenesis inhibitors targeting either one or a few pro-angiogenic factors or a range of downstream signaling molecules provide clinical benefit, but not without significant side effects. miRNAs are important post-transcriptional regulators of gene expression, and their dysregulation has been associated with tumor progression, metastasis, resistance, and the promotion of tumor-induced angiogenesis. In this mini-review, we provide a brief overview of the current anti-angiogenic approaches, their molecular targets, and side effects, as well as discuss existing literature on the role of miRNAs in angiogenesis. As we highlight specific miRNAs, based on their activity on endothelial or cancer cells, we discuss their potential for anti-angiogenic targeting in cancer as adjuvant therapy and the importance of angiogenesis being evaluated in such combinatorial approaches.

Keywords: angiogenesis, adjuvant therapy, miRNAs, drugs, combinatorial

INTRODUCTION

Angiogenesis is the physiological process for new blood vessel development from pre-existing ones. It is a highly coordinated, multistage process that occurs in physiological conditions, such as wound healing, the female reproductive cycle, and embryonic development, and many pathological conditions, including cancer. The angiogenic outcome highly depends on the balance of growth factors and angiogenesis inhibitors. Dysregulation of this balance leads to the increased or limited vascular network identified in a series of pathologies, such as retinopathies, inflammatory disorders, cardiovascular disorders, and tumors (1–3).

The rapid growth of tumor cells requires the continuous supply of oxygen and nutrients, the diffusion of which in vivo is significantly limited at 100-500 microns from the nearest capillary. Solid tumors cannot grow more than 2-3 mm in diameter and thus become dormant without vascular support (4, 5). The rapid proliferation of the tumor cells leads to their distant localization from the nearest capillary and the induction of hypoxia, a major driver of angiogenesis. Hypoxia leads to the secretion of many growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), cytokines, such as interleukin 8 (IL-8), and other pro-angiogenic...
mediators, such as sphingosine-1 phosphate (SIP), leading to the proliferation, migration and tumor-like formation of the nearby endothelial cells (5–8). The newly formed tumor vessels are markedly distinct from the normal capillaries due to their chaotic structure characterized by the absence of proper orientation, the limited pericyte and smooth muscle cell coverage, blunt capillary ends, increased leakiness, and limited perfusion. The increased leakiness provides fertile ground for tumor cell dissemination and metastasis, while the limited mural support often leads to their collapse due to the higher interstitial pressure of the tumoral area, increasing further the hypoxic conditions (3, 5, 9).

Targeting the tumor vascular network with anti-angiogenic therapy, despite the excellent preclinical results and the high potential these provided, did not meet the expectations in the clinic, with ephemeral results and not significant benefit in overall survival in most tumors. A prominent reason for this is considered the induction of compensatory mechanisms due to increased hypoxia upon anti-angiogenic treatment, which drives the overexpression of other pro-angiogenic factors, blocks immune functionality, and limits the perfusion of cytotoxic therapies (10, 11). During the last decade, the notion of vascular normalization as an outcome of anti-angiogenic therapy has risen, which can be achieved within a short therapeutic window during anti-angiogenic therapy. Tumor vascular normalization is expected to induce the integrity of the tumor vessels providing increased mural cell support, limited leakiness, inhibition of trans-endothelial cancer cell migration and metastatic incidence, and higher perfusion, which would limit the hypoxic areas and accommodate improved anti-cancer drug delivery in the tumoral area (12–14). The majority of the studies have focused on VEGF inhibition, the main target of anti-angiogenic therapies. A precise dosage of VEGF inhibitors has been demonstrated to inhibit vascular permeability by tightening cell-to-cell contacts and recruiting pericytes. VEGF is not the sole mediator of vascular permeability, as an increasing volume of data has highlighted the involvement of other molecular players and pathways, such as Angiopoietin-2, Semaphorin 3A, nitric oxide, superoxide dismutase-3, Notch, WNT, platelet-derived growth factor-B (PDGF-B) and bone morphogenetic protein (MBP) signaling in this process (10, 11, 13, 15, 16).

Nucleic acid-based therapeutics have attracted attention for the treatment of several diseases, including cancer (17, 18), inflammation (19), or the development of vaccines, such as against SARS-CoV-2 (i.e. COVID-19) (20–22). Among the different types of nucleic acids currently under research, miRNAs, natural molecules produced by the cells frequently transcribed along with protein-expressing genes (23, 24), are commonly dysregulated in diseases, such as cancer, inflammation, and others. Not surprisingly, miRNAs were recognized as potential prognostic and diagnostic markers in cancer (23–26). More importantly, as miRNAs are small, non-coding RNAs that utilize the cell’s RNA interference mechanism to regulate multiple gene expressions, miRNAs are evaluated as therapeutic tools against cancer (23). An increasing body of literature focuses on dysregulated miRNAs for their properties as tumor suppressors or oncogenes, and on their action to either suppress or activate tumor-promoting pathways (23). Exogenous delivery of miRNA constructs, similarly to the exogenous delivery of siRNAs, aims to replace or correct observed miRNA dysregulations. Unlike siRNAs though, miRNA replacement therapies induce the expression or increase the levels of nucleic acid sequences naturally occurring in the cells, which should have an indistinguishable effect on the endogenous miRNAs (23, 24). Though this approach has limitations, the exogenous delivery of miRNAs should induce a strong beneficial effect on cells associated with the disease (i.e., cancer cells or cells of the tumor microenvironment with dysregulated miRNA expression) while having minimal effects on normal cells (i.e., absence of dysregulation) (27).

Representatively, miR-34a is characterized as a master tumor suppressor against multiple cancer types, capable of regulating proliferation, migration (28), apoptosis (29), metastasis, senescence, differentiation, and immune responses (30). Similarly, the clinical potential and translation of other miRNAs are currently undergoing. We are not outlining these studies, as several review publications focus on the current and past clinical trials [indicatively, refer to: (31–33)]. As miRNAs are expressed in all types of cells, miRNAs regulate vascular development and angiogenesis in endothelial cells (EC). Landskroner-Eiger et al. (34) summarized the importance of miRNAs in angiogenesis from the perspective of the Dicer enzyme. Dicer enzyme is a key component in the biogenesis of miRNAs, and several studies evaluated the effect of Dicer deletion/inactivation in normal vascular development. Dicer activity affected angiogenesis, attributed to defective miRNA expression, dysregulating the expression of VEGF and its receptors. As miRNA dysregulation in cancer has been well documented (35) either through cell-to-cell communication between cancer cells and EC or EC intracellular miRNA dysregulation, utilization of miRNAs as targets or regimens can benefit cancer treatments through regulation of EC function and formation of blood vessels (36, 37). There is an increasing interest in the combination of anti-angiogenic agents with traditional chemotherapeutics and several clinical trials pursued that approach (2, 38). We sought to explore the use of miRNAs for cancer treatment due to their ability to regulate angiogenesis and focus on their potential and utilization as adjuvant therapies with chemotherapeutics because of their anti-angiogenic properties. Although there is a substantial body of literature focusing on miRNAs and angiogenesis, limited work exists on their combination with chemotherapeutics predominately due to their anti-angiogenic properties. Here, we present miRNAs that are frequently studied due to their angiogenesis-inhibiting capacity and have been combined with traditional chemotherapeutics, even when the utilization of these miRNAs was not because of their anti-angiogenic properties.

**CURRENT ANTI-ANGIOGENIC THERAPIES**

Not long after its discovery, VEGF was characterized as a principal vascular regulator (39, 40). VEGF haploinsufficiency led to embryonic lethality due to impaired angiogenesis and
blood vessel formation (41, 42). The striking impact on angiogenesis, vascular morphology, and functions upon VEGF inhibition or deficiency, along with its overexpression in most solid tumors, including lung, breast, liver, and ovarian cancers, brought it to the frontline of anti-angiogenic targets, where it remains till today. The first FDA-approved anti-angiogenic drug was bevacizumab, a monoclonal antibody against VEGF (43, 44). Bevacizumab, combined with chemotherapy, improved overall survival in colorectal cancer (45) and soon provided encouraging results when tested in ovarian, cervical, non-small cell lung cancers, and mesothelioma. Today, bevacizumab is FDA-approved for colorectal cancer, non-small cell lung cancer, renal cell carcinoma, cervical, fallopian tube cancer, peritoneal cancer, and glioblastoma, whereas it failed to provide clinical benefit in the majority of the other cancer types, including breast cancer, for which the FDA approval lasted for a short period (2). Apart from bevacizumab, other antibody-based anti-angiogenic inhibitors are ramucirumab and aflibercept, which target VEGF receptor 2 (VEGFR2) or VEGF-A, VEGF-B and placental growth factor (PIGF), respectively. The rest of the angiogenesis inhibitors include small molecule or tyrosine kinase inhibitors that target one or more signaling pathways. Some of these tyrosine kinase inhibitors, such as sunitinib and regorafenib, inhibit a wide range of molecular targets and downstream mediators. The current, clinically administered anti-angiogenic inhibitors, their molecular targets, and the approved cancer types are presented below (2, 46–54):

- **Bevacizumab**, targeting VEGF-A, for glioblastoma, colorectal, cervical, fallopian tube, peritoneal, non-small cell lung cancers and renal cell carcinoma.
- **Ramucirumab**, targeting VEGFR2, for gastric, gastroesophageal junction, non-small cell lung and colorectal cancers.
- **Aflibercept**, targeting VEGF-A,-B and PIGF, for colorectal cancer.
- **Axitinib**, targeting VEGF-A,-B and PIGF, for colorectal cancer.
- **Cabozantinib**, targeting VEGFR1-3, receptor tyrosine kinase (KIT), tropomyosin receptor kinase B (TRKB), anexelekto receptor tyrosine kinase (AXL), Rearranged during transfection (RET), tyrosine kinase MET, Fms-like tyrosine kinase-3 (FLT-3), TEK receptor tyrosine kinase (TIE2), for hepatocellular and renal cell carcinomas, and Medullary thyroid cancer.
- **Everolimus**, targeting mammalian target of rapamycin (mTOR), for breast, pancreatic, gastrointestinal, and lung cancers, Renal cell and subependymal giant cell carcinomas.
- **Lenalidomide**, targeting Ikaros family zinc finger protein 1,3 (IKZF1,3), E3 ubiquitin ligase, for follicular, mantle cell and marginal zone lymphomas, and multiple myeloma.
- **Lenvatinib**, targeting VEGFR1-3, for endometrial, hepatocellular and renal cell carcinomas and Thyroid cancer.
- **Pazopanib**, targeting VEGFR1-3, PDGF receptor-α/β (PDGF-α/β), fibroblast growth factor receptor 1,2 (FGFR1,2), c-KIT, for renal cell and soft tissue carcinomas.
- **Sorafenib**, targeting VEGFR1-3, PDGF-β, FLT-3, c-KIT, RAF kinases, for hepatocellular and renal cell carcinomas and thyroid cancer.
- **Sunitinib**, targeting VEGFR1-3, PDGFR-α/β, KIT, FLT-3, colony-stimulating factor receptor Type 1 (CSF-1R), RET, for gastrointestinal stromal and pancreatic cancers and renal cell carcinoma.
- **Regorafenib**, targeting VEGFR1-3, KIT, PDGFR-α/β, FGFR1,2, TIE2, discoidin domain receptor tyrosine kinase 2 (DDR2), tropomyosin receptor kinase A (TRKA), Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, Abelson tyrosine kinase 1 (ABL), for gastrointestinal stromal and colorectal cancers and hepatocellular carcinoma.
- **Thalidomide**, targeting tumor necrosis factor-α (TNF-α), for multiple myeloma.
- **Vandetanib**, targeting VEGFR, epidermal growth factor receptor (EGFR), RET, for medullary thyroid cancer.

**LIMITATIONS AND SIDE EFFECTS OF ANTI-ANGIOGENIC THERAPIES**

As seen above, most anti-angiogenic drugs are targeting VEGF or VEGFR, either solely or in combination with other growth factor receptors or downstream kinases. Their administration provides encouraging clinical benefit; however, their application is not without side effects. The two most critical side effects of anti-angiogenic therapy are the induction of tumor aggressiveness along with metastatic potential and the tumor angiogenesis relapse due to the development of resistance mechanisms. The induction of tumor aggressiveness and metastatic potential upon anti-angiogenic therapy is still under debate, as it has been reported in preclinical models, but not always verified in other studies, demonstrating the variability of this phenomenon (55–57).

One of the limiting factors of anti-angiogenic therapy in cancer is that since cancer cells are not eradicated, as they do not consist the target of anti-angiogenic therapy, anti-angiogenic drugs have to be administered over long periods. The ephemeral outcome of anti-angiogenic therapy and the need for prolonged treatment eventually lead to the development of resistance upon anti-angiogenic inhibition. Resistance can be driven by the tumor cells, the stroma, immune cells, or endothelial progenitors, is mediated by the upregulation of alternative pro-angiogenic mediators, and presents cancer type- and patient-specific variability (8, 58).

Systemic anti-angiogenic drug administration, both in the case of antibody-specific VEGF inhibition and a wide range of tyrosine kinase inhibitors, can lead to organ- or tissue-specific side effects (59). A meta-analysis of five randomized clinical trials of metastatic colorectal, breast, and non-small cell lung cancers highlighted the risk of a thromboembolic event as another side effect of bevacizumab treatment in combination with chemotherapy (60). Cardiomyopathy and congestive heart failure have also been reported as side effects of anti-angiogenic inhibitors (61). Although the exact mechanism for cardiomyopathy and congestive heart failure upon VEGF signaling blockade has not yet been fully delineated, the current notion is that existing conditions depleting the vascular
reserve, such as hypertension and coronary artery disease, may be considered risk factors for cardiotoxicity with VEGF signaling inhibitors, while reduced nitric oxide production, mitochondrial dysfunction and pericyte population depletion have been attributed as potential mechanisms (62, 63). It has been further preclinically demonstrated that abrogation of the physiological VEGF activity can result in increased systemic (and coronary) vascular resistance and decreased cardiac output per se, which is the typical reason for cardiomyopathy development. Moreover, the roles of chemotherapy or radiation therapy as concomitant factors in VEGF blockade-induced cardiotoxicity have been further reported (63, 64).

Two well-known side effects of anti-angiogenic therapy that go hand in hand are the increased rate of hemorrhage and the inhibited wound healing process, both of which are determining factors for the timing of surgical procedures (65). Pulmonary hemorrhage with fatal outcome has been reported for non-small cell lung cancer patients with different anti-angiogenesis inhibitors, such as bevacizumab, ramucirumab, sunitinib, axitinib, and motesanib. A small percentage of gastrointestinal tumor patients developed bleeding at the tumor sites, while central nervous bleeding has also been reported (61, 65). Impaired wound healing is a common issue. Angiogenesis is a pivotal part of the wound healing process, mediated by VEGF and other growth factors, thus is expected that VEGF inhibition hampers the wound healing process. As an alternative, milder anti-angiogenic treatments have been proposed to overcome this issue (66). To avoid wound healing deficiency of the surgical area anti-angiogenic treatment has to be terminated for at least four weeks before the surgical procedure so that the body will “wash out” the drug’s effects (61, 65).

The above demonstrate the impact and role of angiogenic factors in physiological vascular functions, the interdependence of the primary tumor and the tumor microenvironment, the need for highly targeted, vascular-specific anti-angiogenic approaches, and the consideration of anti-angiogenic therapies specifically targeting aberrant angiogenesis, without affecting regular angiogenic functions.

MiRNA THERAPEUTICS AND THEIR ADJUVANT POTENTIAL AGAINST ANGIOGENESIS

As research on miRNAs rapidly proliferates, miRNAs’ contribution in tumor suppression via anti-angiogenic function presented multifaceted therapeutic potentials for these molecules. miRNAs have primarily been studied for their activity as single molecules against cancer (17, 35, 67). With numerous miRNAs being able to regulate cell functions and pathways, the number of potential mechanisms of action of miRNAs in angiogenesis correlates to the potential pathways associated with angiogenesis. Nonetheless, similarly to traditional anti-angiogenic approaches, studies on miRNAs and angiogenesis have primarily focused in known, more traditional angiogenic pathways. Thus, miRNAs studies focus on angiogenic factor receptors or signaling molecules in ECs to inhibit tumor angiogenesis (68), among them more prominently being VEGF, VEGFR and PDGFR (69–71). As numerous dysregulated miRNAs have been identified in tumor samples, here, we will present a few of the miRNAs with explicit action on angiogenesis and their identified molecular targets.

miR-34a, a master tumor suppressor, is one of the best-studied miRNAs, and, hence, its activity on tumor cells and cells of the tumor microenvironment has been thoroughly evaluated. Several studies have reported on miR-34a’s ability to inhibit tumor angiogenesis. This activity takes place via multiple approaches, including the inhibition of the Silent Information Regulator 1 (Sirt1) expression, increase of the expression of acetylated Forkhead Box O1 (FoxO1) transcription factor, Notch1 targeting, and the p53 protein in endothelial progenitor cells and human cancer cells (72–75). miR-34a downregulation in EC induced BCL-2 overexpression and inhibition of apoptosis, while miR-34a upregulation suppresses tumor angiogenesis, EC proliferation, migration, and tube formation (76, 77). miR-34a has also extensively been studied in combination with several chemotherapeutics, such as cisplatin (78, 79), doxorubicin (80), sorafenib (81), and paclitaxel (82), among others. Despite the well-studied anti-angiogenic properties of the miRNA, we did not find research on its combination with a chemotherapeutic agent based solely due to its anti-angiogenic properties, rather than miR-34a’s activity on the tumor cells.

Similarly, the miR-29 family, miR-29a, miR-29b, and miR-29c, are downregulated in various cancers, such as endometrial carcinoma, hepatocellular carcinoma, gastric cancer, and breast cancer (83–86). miR-29b overexpression inhibits angiogenesis and tumorigenesis in vivo and weakens tube formation, cell proliferation, and migration in vitro (83). miR-29b prevented tumor angiogenesis by targeting AKT3 and inhibited Akt3-mediated VEGF and C-myc activations (86). In a gastric cancer mouse model, miR-29a/c prevented tumor growth, tube formation, and suppressed angiogenesis by suppressing VEGF-A expression (87). Similar to miR-34a, members of the miR-29 family have been attributed with tumor-suppressive properties and evaluated with several chemotherapeutic agents, such as cisplatin (88), and paclitaxel (89), among others. Of interest, miR-29a has been reported to contribute to doxorubicin resistance in breast cancer cells (90) and inhibit doxorubicin resistance in colon cancer cells (91). Li et al. (92) reported that cisplatin treatment induces upregulation of miR-29b, which suppressed invasion and angiogenesis of the cancer cells in vitro and inhibited tumor growth and neovascularization in vivo. The authors demonstrated that ectopic expression of miR-29b via intravenous administration in a subcutaneous xenograft mouse model of cervical cancer (HeLa cells) inhibited tumor growth and VEGF expression, corresponding to a decrease in vessel formation, although the authors did not evaluate this activity with the co-administration with cisplatin.

miR-221 and miR-222 modulated the angiogenic behavior of human umbilical vein endothelial cells (HUVECs) through the
regulation of c-Kit expression (93). As these miRNAs were among the most abundantly expressed miRNAs in ECs (94), Nicoli et al. reported that miR-221 is essential for angiogenesis, in the zebrafish model (95). In human venous or lymphatic endothelial cells, miR-221 has been shown to inhibit angiogenesis (93, 96–98). miR-221 has been identified as oncogenic in pancreatic cancer cells (99), glioblastoma (100), breast cancer (101), and lung cancer (102), among others. miR-221/222 have also been associated with increased chemoresistance to cisplatin in ovarian (103) and breast cancer cells (104). Similar results have been reported with Adriamycin (doxorubicin) (105, 106), 5-fluorouracil (107), and paclitaxel (108). Representatively, in vivo analysis of downregulation of miR-221/222 through local injection in a breast cancer mouse model enhanced the cisplatin’s tumor growth inhibition capacity, but no analysis on tumor vasculature took place (104). In fact, in the in vivo studies of the miRNA-drug combinations, angiogenesis was not evaluated. This complex behavior is a representative example of the multi-faceted activity of miRNAs, which can be cancer- or cell-type-specific, and their combination with drugs can extend outside of the tumor cells, to the tumor microenvironment.

The expression of the most potent angiogenesis modulators in different tumors in terms of downstream targets of miRNAs has been extensively studied. Multiple miRNAs have been found to target VEGF since it is the most potent trigger for angiogenesis. miR-20 (109), miR-29b (110), miR-93 (111, 112), miR-126 (113, 114) target the 3’-UTR region of VEGF-A mRNA. Following, we provide representative examples of miRNAs with anti-angiogenic properties that also demonstrated anti-tumorality. miR-27b (115, 116) and miR-128 (69) suppress tumor progression and angiogenesis by targeting VEGF-C. miR-125b suppressed EC tube formation by inhibiting E-cadherin (117). miR-192 targets EGR1 and HOXB9, leading to anti-tumor and anti-angiogenic activity in human ovarian epithelial tumors (118). miR-200 family inhibited angiogenesis through direct and indirect mechanisms by targeting interleukin-8 (IL8) and CXCL1 secreted by the tumor endothelial and cancer cells (119). Overexpression of miR-190 inhibited EMT and angiogenesis by inactivating AKT-ERK signaling (120). miR-206 inhibited HGF-induced epithelial-mesenchymal transition (EMT) and angiogenesis in lung cancer, by suppressing Met/PI3k/Akt/mTOR signaling (121). miR-135a promoted cell apoptosis and inhibited cell proliferation, migration, invasion, and tumor angiogenesis by targeting the IGF-1 gene through the IGF-1/PI3K/Akt signaling pathway in non-small cell lung cancer (NSCLC) (122). Finally, miR-143 and miR-506, alone and in combination have been reported to affect angiogenesis, by inhibiting tube formation in HUVEC cells, while causing apoptosis to lung cancer cells (123).

As the VEGF family and its downregulation have been implicated in drug resistance in tumor cells (124–126), it is reasonable to predict that miRNAs with the capacity to target members of the VEGF family will become part of a cell-sensitization goal for specific chemotherapeutics. Due to this reason alone, studies of miRNA-chemotherapeutic drugs combinatorial use for cancer treatment have the potential to proliferate in the future (Figure 1). One representative example would be miR-126, where Zhu et al., (127) demonstrated that miR-126 decreased the minimum inhibitory concentration of Adriamycin and Vincristine by targeting VEGF-A. In Table 1, we present a short list of studies with miRNAs with known anti-angiogenic activity in combination with chemotherapeutics.

Illustratively, Wang et al. (155) studied the combination of miR-30a-5p with gefitinib to overcome drug resistance via regulation of the insulin-like growth factor receptor-1 (IGF1R) and hepatocyte growth factor receptor signaling pathways in NSCLC both in vitro and in vivo. Liang et al. (156) formulated exosomes to simultaneously deliver the anticancer drug 5-FU and a miR-21 inhibitor oligonucleotide (miR-21i) to 5-FU-resistant colon cancer cells. This approach reversed drug resistance and significantly enhanced the drug’s cytotoxicity in 5-FU-resistant colon cancer cells, compared to the single treatment with either miR-21i or 5-FU in an in vivo mouse model. Similarly, miR-375-3p, which has been reported to suppress tumorigenesis and reverse chemoresistance in colon cancer, along with 5-FU co-delivered in lipid-coated calcium carbonate nanoparticles were used to study the role of miR-375-3p in 5-FU-resistance in colorectal cancer (157, 158).

DISCUSSION

It is evident that miRNAs can have a significant impact on angiogenesis and cancer treatment. As our knowledge on miRNA activity expands, the highly complex interaction between miRNA and angiogenesis due to autocrine or paracrine interactions will dictate the future potential of the miRNAs as therapeutic tools. One major hurdle of anti-cancer therapies, including the anti-angiogenic therapies described above, is the off-target effects due to non-specific tissue- or cell-targeting. This hurdle is further exacerbated with the miRNAs, as the tumor type and the multifaceted activity of the miRNAs can have synergistic or antagonistic therapeutic outcomes through the tumor microenvironment. Thus, the in vivo evaluation of the miRNAs needs to expand outside the tumor cell growth and incorporate aspects, such as angiogenesis.

Another parameter to be taken into account for miRNA-based therapies is the promiscuous binding of high miRNA dose, causing multiple off-target effects. This significant hurdle of miRNA-based treatments can be resolved by miRNA cooperativity and lower miRNA doses, while it is noteworthy that the final outcome of the targets of the cooperating genes strongly depends on the cellular environment (159).

miRNA delivery has been challenging by itself, due to the nucleic acids’ rapid elimination from the circulation, the abundance of nuclease in vivo, and the need for a carrier for the large hydrophilic nucleic acid constructs to enter the cells (23, 24). The added complexity of the required cell type drug delivery specificity presents an additional challenge, which needs to be potentially overcome in the presence of an already impaired tumor vascular system (26). Several novel delivery carriers have been developed and studied for the delivery of miRNAs. These
include micelles, polymeric nanocarriers, lipid-based carriers, viruses, inorganic carriers, and systems with long-circulating properties and/or active targeting to receptors over-expressed in cancer cells (23). Although the goal of a single organ and single-cell type targeting maybe be understandably impractical, these methodologies have provided significant benefits for minimizing off-target effects, increasing accumulation in the tumor, and preferentially increasing drug/nucleic acid concentration in specific cell types. Nonetheless, off-target effects will persist, even due to cell-to-cell communication.

This perspective has a significant impact when studying miRNA-drug combinations. Although in vitro analysis is fundamental to evaluate the synergistic/antagonistic behavior of a miRNA and a drug, the effect of the co-delivery of the miRNA-drug combination in vivo should take into consideration the anti-angiogenic properties of the miRNAs. Of course, this

| miRNA          | Drug             | Cancer                          | References |
|----------------|------------------|---------------------------------|------------|
| miR-34a        | Doxorubicin      | Hepatocellular carcinoma        | (80)       |
|                | Paclitaxel       | Osteosarcoma                    | (128)      |
|                | Docetaxel        | Breast cancer                   | (132)      |
|                | 5-Fluorouracil   | Colorectal cancer               | (133, 134) |
| Let-7c-5p      | 5-Fluorouracil   | Hepatocellular carcinoma        | (135)      |
| Anti-mIR-21    | Sunitinib        | Pancreatic ductal adenocarcinoma| (137)      |
| miR-145        | Sunitinib        | Breast cancer                   | (139)      |
| miR-205        | Gemcitabine      | Pancreatic cancer               | (140)      |
| miR-129        | 5-Fluorouracil   | Colorectal cancer               | (141)      |
| miR-497        | 5-Fluorouracil   | Colorectal cancer               | (142)      |
| miR-34a and miR-27b | Docetaxel | Prostate cancer               | (143)      |
| miR-29b        | Dihydroarctemin | Cholangiocarcinoma              | (144)      |
| miR-221        | Doxorubicin      | Glioma                          | (145)      |
| miR-192-5p     | Doxorubicin      | Breast cancer                   | (146)      |
| miR-378a       | Sorafenib        | Liver cancer                    | (147)      |
| miR-122, miR-338-3p | Sorafenib | Hepatocellular carcinoma        | (148)      |
| miR-193a       | Taxol            | Colorectal cancer               | (149)      |
| miR-143        | Cisplatin        | Cervical cancer                 | (150)      |
| miR-29         | Cisplatin        | Ovarian cancer                  | (151)      |
| miR-7          | Doxorubicin and Temozolomide | Glioma, Cervical carcinoma, Papillary thyroid | (152) |
| miR-506-3p     | Cisplatin        | Ovarian cancer                  | (153)      |
| miR-135 and miR-138 | 5-Fluorouracil | Coton cancer, pancreatic cancer, cervical cancer | (154) |

*All miRNAs listed have tumor-inhibiting properties.*
easily expands to other aspects of the tumor microenvironment, such as macrophages, though immunosuppressed animal models will present challenges for such evaluation.

Though we recognize that there might be published research on miRNA-drug combination focusing on angiogenesis we overlooked, it is apparent from our analysis that currently the anti-angiogenic aspect of miRNAs co-delivered with drugs is not the primary focus, or is not studied in detail or at all, even for miRNAs with known anti-angiogenic properties. Simply stated, the question arises on how much of the enhanced anti-tumoral activity of miRNA-drug combinations can be attributed to the alteration of tumor cell behavior, angiogenesis, or both. Finally, another important aspect is the toxicity potential from the miRNAs. We described above the side effects attributed to the clinically used anti-angiogenic therapies, which have a clinical history with well-defined side effects. In contrast, miRNAs have not achieved clinical translation to the same extent, and, thus, similar or other side effects may not yet have become apparent. Nonetheless, the utilization of dysregulated miRNAs, their property of being natural cell products, and the development of novel nanocarriers provide significant advantages to overcome side-effects, commonly present in traditional anti-angiogenic therapies (160). In conclusion, miRNAs are fundamentally important targets and tools for cancer therapy. They have significant potential, based alone on their multifaceted activities on the tumor cells and tumor vascular microenvironment.

Identification of miRNAs with combined anti-angiogenic and anti-tumoral effects can provide significant advantages in cancer treatment, alone or in combination with clinically used chemotherapeutics.

AUTHOR CONTRIBUTIONS

BL, SP, CM, and GM contributed to the conception of the article, wrote and revised the final manuscript and agreed on its submission to this journal. All authors contributed to the article and approved the submitted version.

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