Targeting oncomiRNAs and mimicking tumor suppressor miRNAs: New trends in the development of miRNA therapeutic strategies in oncology (Review)

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Abstract. MicroRNA (miRNA or miR) therapeutics in cancer are based on targeting or mimicking miRNAs involved in cancer onset, progression, angiogenesis, epithelial-mesenchymal transition and metastasis. Several studies conclusively have demonstrated that miRNAs are deeply involved in tumor onset and progression, either behaving as tumor-promoting miRNAs (oncomiRNAs and metastamiRNAs) or as tumor suppressor miRNAs. This review focuses on the most promising examples potentially leading to the development of anticancer, miRNA-based therapeutic protocols. The inhibition of miRNA activity can be readily achieved by the use of miRNA inhibitors and oligomers, including RNA, DNA and DNA analogues (miRNA antisense therapy), small molecule inhibitors, miRNA sponges or through miRNA masking. On the contrary, the enhancement of miRNA function (miRNA replacement therapy) can be achieved by the use of modified miRNA mimetics, such as plasmid or lentiviral vectors carrying miRNA sequences. Combination strategies have been recently developed based on the observation that i) the combined administration of different antagomiR molecules induces greater antitumor effects and ii) some anti-miR molecules can sensitize drug-resistant tumor cell lines to therapeutic drugs. In this review, we discuss two additional issues: i) the combination of miRNA replacement therapy with drug administration and ii) the combination of antagomiR and miRNA replacement therapy. One of the solid results emerging from different independent studies is that miRNA replacement therapy can enhance the antitumor effects of the antitumor drugs. The second important conclusion of the reviewed studies is that the combination of anti-miRNA and miRNA replacement strategies may lead to excellent results, in terms of antitumor effects.

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Abbreviations: miRNAs or miRs, microRNAs; PNA, peptide nucleic acids; CTCs, circulating tumor cells; EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition; CML, chronic myelogenous leukemia; CRC, colorectal carcinoma

Key words: microRNAs, peptide nucleic acids, miRNA replacement therapy, antagomiR, epithelial-mesenchymal transition, metastasis, miR-124

Contents

Introduction

MicroRNAs (miRNAs or miRs) are a family of small (19-25 nucleotides in length) non-coding RNAs that have a key role in the regulation of gene expression through the inhibition or the reduction of protein synthesis following mRNA complementary sequence base pairing (1-4). A single or multiple mRNAs can be targeted at the 3' untranslated region (3'UTR),

coding sequence (CDS) or 5' untranslated region (5'UTR) sequence, and it is calculated that >60% of human mRNAs are recognized by miRNAs (1-4). The miRNA/mRNA interaction occurs at the level of the RNA-induced silencing complex (RISC) and causes translational repression or mRNA degradation, depending on the degree of complementarity with target mRNA sequences (5-8). Since their discovery and first characterization, the number of human miRNAs identified and deposited in the miRBase databases (miRBase v.21, www.mirbase.org) has increaed (it is >2,500) (9-16) and the research studies on miRNAs have confirmed the very high complexity of the networks constituted by miRNAs and RNA targets (17-22).

Alterations in miRNA expression have been demonstrated to be associated with different human pathologies, and guided alterations of specific miRNAs have been suggested as novel approaches for the development of innovative therapeutic protocols (23,24). Studies have conclusively demonstrated that miRNAs are deeply involved in tumor onset and progression, either behaving as tumor-promoting miRNAs (oncomiRNAs and metastamiRNAs) or as tumor suppressor miRNAs (25,26). In general, miRNAs able to promote cancer target mRNAs coding for tumor suppressor proteins, whereas miRNAs exhibiting tumor suppressor properties usually target mRNAs coding oncoproteins (see the scheme depicted in Fig. 1A). This has a very important implication in diagnosis and/or prognosis, including the recent discovery that the pattern of circulating cell-free miRNAs in serum allows us to perform molecular analyses on these non-invasive liquid biopsies with deep diagnostic and prognostic implications. This research field has confirmed that cancer-specific miRNAs are present in extracellular body fluids, and may play a very important role in the crosstalk between cancer cells and surrounding normal cells (27-32).

Interestingly, the evidence of the presence of miRNAs in serum, plasma and saliva supports their potential as an additional set of biomarkers for cancer. The extracellular miRNAs are protected by exosome-like structures, small intraluminal vesicles shed from a variety of cells (including cancer cells), with a biogenesis connected with endosomal sorting complex required for transport machinery in multivesicular bodies (29). For instance, miR-141 and miR-221/222 are predicted biomarkers in liquid biopsies from patients with colon cancer (33,34).

On the other hand, tumor-associated miRNAs are suitable targets for intervention therapeutics, as previously reported (35-44) and summarized in Fig. 1B. The inhibition of miRNA activity can be readily achieved by the use of miRNA inhibitors and oligomers, including RNA, DNA and DNA analogues (miRNA antisense therapy) (45-47), small molecule inhibitors, locked nucleic acids (LNAs) (48-53), peptide nucleic acids (PNAs) (54-57), morpholinos (58-60), miRNA sponges (61-67), mowers (68) or through miRNA masking that inhibits miRNA function by masking the miRNA binding site of a target mRNA using a modified single-stranded RNA complementary to the target sequence (69-75). On the contrary, the enhancement of miRNA function (miRNA replacement therapy) can be achieved by the use of modified miRNA mimetics, either synthetic, or produced by plasmid or lentiviral vectors carrying miRNA sequences (76-81).

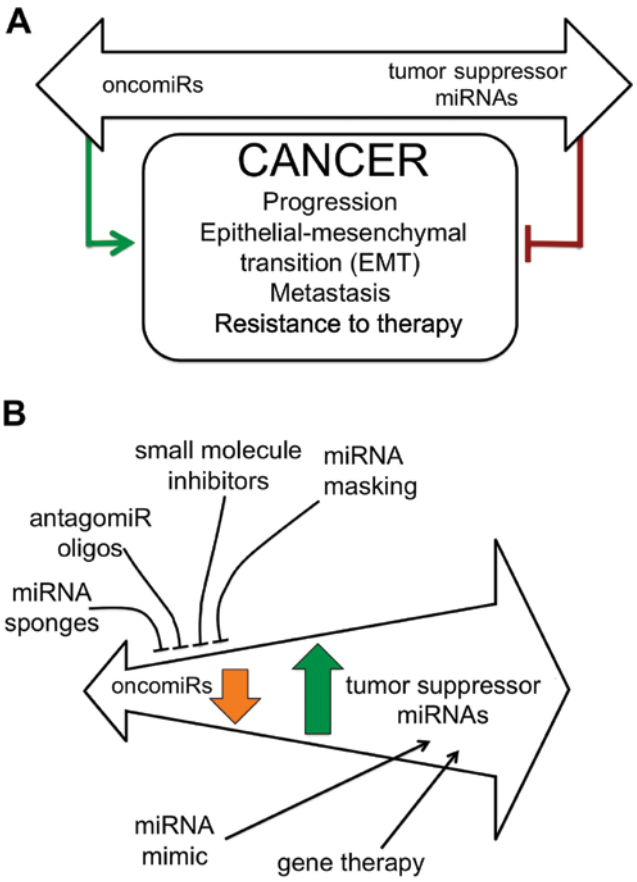

Figure 1. (A) Scheme outlining the ability of miRNAs to promote cancer and metastasis (green arrowed line) or to suppress mRNAs coding oncoproteins (red line). (B) Examples of proposed approaches for the development of therapeutic protocols to modulate the biological activity of miRNAs involved in cancer. The objectives of these molecular interventions are the downregulation of oncomiRNAs and metastamiRNAs (orange arrow) or the upregulation/mimicking of onco-suppressor miRNAs (green arrow). Modified from Ghelani *et al* (3).

2. Tumor suppressor miRNAs

Several miRNAs exhibit onco-suppressor properties by targeting mRNAs coding oncoproteins (82-105). Therefore, these onco-suppressor miRNAs have been found to be often downregulated in tumors. For instance, Fernandez *et al* (106) recently described the intriguing tumor suppressor activity of miR-340, showing the miR-340-mediated inhibition of multiple negative regulators of p27, a protein involved in apoptosis and cell cycle progression. These interactions with oncoprotein-coding mRNA targets determine the inhibition of cell cycle progression, the induction of apoptosis and growth inhibition. The miR-340-mediated downregulation of three post-transcriptional regulators [Pumilio RNA-binding family member (PUM)1, PUM2 and S-phase kinase-associated protein 2 (SKP2)] correlates with the upregulation of p27. PUM1 and PUM2 inhibit p27 at the translational level, by rendering the p27 transcript available to interact with two oncomiRs (miR-221 and miR-222), while the oncoprotein SKP2 inhibits the CDK inhibitor at the post-translational level by triggering the proteasomal degradation of p27, showing that miR-340 affected not only the synthesis but also the decay

of p27. Moreover their data confirm the recent identification of transcripts encoding several pro-invasive proteins such as c-Met, implicated in breast cancer cell migration, RhoA and Rock1, implicated in the control of the migration and invasion of osteosarcoma cells, and E-cadherin mRNA, involved in the miR-340-induced loss of intercellular adhesion (106 and refs within).

Recently, miR-18a was demonstrated to play a protective role in colorectal carcinoma (CRC) by inhibiting the proliferation, invasion and migration of CRC cells by directly targeting the TBP-like 1 (TBPL1) gene. The onco-suppressor activity of miR-18a in CRC tissues and cell lines was supported by the finding that the content of this mRNA is markedly lower in tumor cells with respect to normal control tissues and cells (107). In addition Xishan *et al* (108) found that miR-320a acts as a novel tumor suppressor gene in chronic myelogenous leukemia (CML) and can decrease the migratory, invasive, proliferative and apoptotic behavior of CML cells, as well as epithelial-mesenchymal transition (EMT), by attenuating the expression of the BCR/ABL oncogene. Furthermore Zhao *et al* (109) demonstrated that miR-449a functions as a tumor suppressor in neuroblastoma by inducing cell differentiation and cell cycle arrest. Finally, Kalinowski *et al* (110) and Gu *et al* (111) demonstrated the significant role of miR-7 in cancer which functions by directly targeting and inhibiting key oncogenic signaling molecules involved in cell cycle progression, proliferation, invasion and metastasis. A partial list of onco-suppressor miRNAs is presented in Table I.

3. OncomiRNAs and metastamiRNAs

miRNAs can act as oncogenes and have been demonstrated to play a causal role in the onset and progression of human cancer (oncomiRNAs) (224-233). Recent findings have nevertheless identified a subclass of miRNAs whose expression is highly associated with the acquisition of metastatic phenotypes and are referred to as miRs endowed with either metastasis-promoting or tumor suppressor inhibitory activities (213,234,235).

Recent data have revealed that miR-25 may act as an onco-miRNA in osteosarcoma, negatively regulating the protein expression of the cell cycle inhibitor, p27. In agreement with this hypothesis restoring the p27 level in miR-25-over-expressing cells was shown to reverse the enhancing effect of miR-25 on Saos-2 and U2OS cell proliferation (236). In addition a recent study published by Siu *et al* (237), describes miR-96 as a potential target of therapeutics for metastatic prostate cancer, demonstrating the enhanced effects in cellular growth and invasiveness of miR-96 in cell lines (AC1, AC3 and SC1) derived from prostate-specific, Pten/Tp53 double knockout mice and confirmed in tissue samples from prostate cancer patients. miR-96 acts as an oncomiR and metastamiR through TGF-β/mTOR signaling, promoting bone metastasis and contributing to a reduced survival rate in prostate cancer (237). Furthermore Xia *et al* (238) demonstrated that the overexpression of miR-1908 significantly decreased the expression of PTEN in glioblastoma cells, one of the most frequently mutated tumor suppressors in human cancer, resulting in an increase in proliferation, migration and invasion. Finally Sachdeva *et al* (239), found that miR-182 targets multiple genes in lung metastasis and regulates intravasation, thus increasing the number of circulating tumor cells (CTCs). Only the simultaneous restoration of miR-182 target genes decreased the number of metastases *in vivo*, demonstrating that a single miRNA can regulate the metastasis of primary tumors *in vivo* by the coordinated regulation of multiple genes. Selected examples of oncomiRNAs and metastamiRNAs are presented in Tables II and III. All these miRNAs act by inhibiting tumor suppressor pathways.

4. Mimicking tumor suppressor miRNAs in miRNA replacement therapy

Using the development of anticancer therapies as a representative field of investigation, the therapeutic strategy based on miRNA replacement is targeted to pathological cells which downregulate onco-suppressor miRNAs playing a role in controlling the expression of mRNAs encoding key oncoproteins. The downregulation of these oncogene-targeting miRNAs is clearly the key step for oncogene upregulation leading to tumor onset and progression. Table IV presents selected examples of miRNA replacement therapy in cancer research and treatment (90-92,94-97,99).

As a first representative example, Fig. 2A presents the major results obtained by Wu *et al* (97), who reported that the *in vivo* restoration of miR-29b may represent an option for lung cancer treatment. To demonstrate the efficacy of this strategy, they developed a cationic lipoplexes (LPs)-based carrier that efficiently delivered miR-29b both *in vitro* and *in vivo*. LPs containing miR-29b (LP-miR-29b) efficiently delivered miR-29b to A549 cells and reduced the expression of the key target, CDK6. In a xenograft murine model, in which LPs efficiently accumulated at tumor sites, the systemic delivery of LP-miR-29b increased miR-29b expression in tumors, down-regulated CDK6 mRNA expression in tumors and, as shown in the upper panels of Fig. 2A, significantly inhibited tumor growth.

A second example of miRNA replacement therapy has been published by Glover *et al* (304), who reported that miR-7-5p (miR-7) reduces cell proliferation *in vitro* and induces G1 cell cycle arrest. The systemic miR-7 administration with delivery vesicles reduced adrenocortical carcinoma (ACC) xenograft growth originating from both ACC cell lines and primary ACC cells. As far as the potential mechanisms of action, miR-7 was demonstrated to target Raf-1 proto-oncogene serine/threonine kinase (RAF1). Additionally, miR-7 therapy *in vivo* led to the inhibition of cyclin dependent kinase 1 (CDK1) (304). Two other methods have also been used to successfully deliver miR-7 *in vivo* to treat cancer. In a study by Babae *et al* (305), a miR-7 mimic was systemically delivered using clinically viable, biodegradable, targeted polyamide nanoparticles. This strategy led to the successful inhibition of tumor growth and vascularisation in a glioblastoma xenograft model system. In an earlier study, Wang *et al* (306) was able to inhibit glioma xenograft growth and metastasis using a plasmid based miR-7 vector systemically delivered by encapsulation in a cationic liposome formulation.

Moreover, Cortez *et al* (307) revealed a novel function of miR-200c, a member of the miR-200 family, in regulating intracellular reactive oxygen species signaling. They used a lung cancer xenograft model to demonstrate the therapeutic

Table I. miRNAs exhibiting tumor suppressor functions.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-1	Head and neck squamous cell carcinoma (HNSCC), prostate cancer	Inhibition of cell proliferation, invasion, migration and promotion of apoptosis and cell cycle arrest; affected cellular organization of F-actin and impaired tumor cell invasion and filopodia formation	TAGLN2, FN1, LASP1, XPO6, TWIST1, EGFR	Nohata *et al* (112); Hudson *et al* (113); Chang *et al* (114)
miR-7	Breast, ovarian cancer	Suppression of cell invasion and metastasis; inhibition of the ability of breast CSCs to metastasize to the brain; inhibition of tumor metastasis and reversed EMT in EOC cell lines	SETDB1, KLF4, EGFR through AKT/ERK1/2 pathway	Zhang *et al* (115); Okuda *et al* (116); Zhou *et al* (117)
miR-let-7	Breast, lung, colon, ovarian cancer	Inhibition of invasion and bone metastasis; reduction of tumor growth, negative regulation of cell cycle-related oncogenes	RAS, MYC, HMGA2, Snail	Lee and Dutta (83); Sampson *et al* (86); Trang *et al* (92); Dangi-Garimella *et al* (118); Takamizawa *et al* (119); Shi *et al* (120); Johnson *et al* (121)
miR-9	Gastric cancer	Suppression of invasion metastasis	Cyclin D1, Ets1	Zheng *et al* (122)
miR-15a; miR-16-1	Chronic lymphocytic leukemia (CLL), multiple myeloma, mantle cell lymphoma, prostate cancers, gastric adenocarcinoma	Induction of apoptosis; decreased tumorigenity, evading growth suppressors, resisting cell death	Bcl-2, cyclin D1, WNT3A	Aqeilan *et al* (123); Calin *et al* (124); Pekarsky *et al* (125); Bonci *et al* (126); Kang *et al* (127)
miR-16	Glioblastoma	Repression of endothelial function and angiogenesis	Bmi-1	Chen *et al* (128)
miR-18a	Colorectal cancer	Decrease of cell migration, altered cell morphology, G1/S phase cell cycle arrest, increased apoptosis	CDC42	Humphreys *et al* (129)
miR-25	Prostate cancer	Inhibition of extravasion *in vivo*	αv, α6 integrins	Zoni *et al* (130)
miR-27a	Acute leukemia	Inhibition of cell growth due at least in part, to increased cellular apoptosis	Bax and Bad	Scheibner *et al* (94)
miR-29c	Nasopharyngeal carcinoma	Inhibition of invasion and metastasis	Collagens, Laminin γ1	Sengupta *et al* (131)
miR-29s (miR-29a, miR-29b1, miR-29b2, miR-29c)	Lung cancer, cervical carcinogenesis, cholangiocarcinoma, hepatocellular carcinoma (HCC), mantle cell lymphoma (MCL), melanoma and acute myeloid leukemia (AML) B and T cells	Decrease in cell proliferation and an increase in cell senescence and apoptosis; decreased AML cell growth and impairement of colony formation, longer survival of treated mice; improvement of anti-leukemic activity of decitabine	CDK6, Ppm1d, osteonectin, Mcl-1, KIT, SP1, Bcl-2, DNMT3A, DNMT3B, DNMTs, Tcl-1, extracellular matrix genes, FLT3, Cdc42, p85a	Ugalde *et al* (132); Garzon *et al* (133); Garzon *et al* (134); Huang *et al* (98); Kapinas *et al* (135); Mott *et al* (136); Fabbri *et al* (137); Xiong *et al* (138); Filkowski *et al* (139); Wang *et al* (140); Hu *et al* (141)
miR-30b	Laryngeal carcinoma	Antitumor and pro-apoptotic effect *in vivo* and *in vitro*	p53 via MDM2	Li and Wang (142)
miR-31	Breast cancer, lung adenocarcinoma (stem cells)	Inhibition of multiple steps of metastasis, including invasion, anoikis and colonization	MET-PI3K-Akt, WAVE3	Hou *et al* (143); Valastyan *et al* (144); Sossey-Alaoui *et al* (145)

Table I. Continued.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-33a	Chronic myelogenous leukemia (CML), colon carcinoma	Decelerated cell proliferation; reduced tumor cell proliferation	Pim-1	Thomas *et al* (95); Ibrahim *et al* (91)
miR-33b	Breast cancer lung metastasis, osteosarcoma	Inhibition of stemness, migration, invasion and metastasis	HMGA2, SALL4, Twist1, c-MYC	Lin *et al* (146); Xu *et al* (147)
miR-34a	Breast, lung, colon, kidney, prostate, bladder, pancreatic, bone and lung cancer, and melanoma	Blocking of tumor growth; inhibition of cell migration, invasion and metastasis of cancer cells; suppression of prostate CSCs and metastasis; decrease in the production of the chemokine CCL22; disturbance of the bone metastatic niche	Bcl-2, cyclin D1, cyclin E2, CDK4, CDK6, c-MYC, MET, N-MYC, SIRT1, Fra-1, CD44, CCL44, Tgif2	He *et al* (148); Bommer *et al* (149); Fujita *et al* (150); Leucci *et al* (151); Saito *et al* (152); Wei *et al* (153); Yamakuchi *et al* (154); Lodygin *et al* (155); Wiggins *et al* (90); Yang *et al* (156); Yang *et al* (157); Liu *et al* (158); Krzeszinski *et al* (159)
miR-34b	Breast, ovarian, endometrial cancer	Tumor suppressor in estrogen-dependent cell growth	Cyclin D1 and JAG1 in ER^+/wild-type p53	Lee *et al* (102); Wang *et al* (160)
miR-34c	Breast, ovarian cancer, lung metastasis	Inhibition of cell migration; invasion and lung metastasis	Fra-1	Yang *et al* (156); Yu *et al* (161)
miR-101-3p	Salivary gland adenoid cystic carcinoma	Suppression of cell proliferation, invasion and enhanced chemotherapeutic sensitivity	Pim-1	Liu *et al* (162)
miR-122a	Liver tumor and disease	Reduced disease manifestation and tumor incidence	Klf6	Tsai *et al* (163)
miR-124	Intrahepatic, bladder, colorectal and lung cancer, osteosarcoma, neuroblastoma, glioma	Modulation of the intercellular adhesion of leading cells; inhibition of EMT *in vitro* and suppression of intrahepatic and pulmonary metastasis *in vivo*; suppression of motility and angiogenesis in bladder cancer cells, of migration and invasion of U-2OS and Saos-2 cells	Integrin β1, ROCK2, EZH2, UHRF1, ROR2, MYO10, DNMT3B, PTB/PKM1/ PKM2 cascade	Taniguchi *et al* (164); Huang *et al* (165); Kato *et al* (166); Zheng *et al* (167); Wang *et al* (168); Zhang *et al* (169); Sun *et al* (170); Sun *et al* (171); Chen *et al* (172); Zhang *et al* (173)
miR-125a	Cervical cancer	Suppression of tumor growth, invasion, metastasis	ARID3B, STAT3	Cowden Dahl *et al* (174); Fan *et al* (175)
miR-126	Non-small cell lung cancer cells, breast, thyroid, liver, colorectal cancer, osteosarcoma	Tumor suppressor genes involved in the control of cell proliferation and cell death, cell migration and blood vessel formation; inhibition of cell proliferation, invasion, migration and tumorigenesis; suppression of tumor metastasis and angiogenesis in hepatocellular carcinoma	EGFL7, SLC7A5, ADAM9, IGFBP2, PITPNC1, MERTK, SDF-1α	Sun *et al* (176); Xiong *et al* (177); Wang *et al* (178); Wen *et al* (179); Jiang *et al* (180); Du *et al* (181); Zhang *et al* (182); Png *et al* (183)
miR-128	Glioblastoma, hepatocellular carcinoma, acute lymphoblastic leukemia	Inhibition of angiogenesis and proliferation, inhibition of tumor cell progression	WEE1, p70S6K1, Msi1, E2F3a, Bmi-1, EGFR, PDGFRA, PIK3R1	Shi *et al* (184); Wuchty *et al* (185); Zhang *et al* (186); Huang *et al* (187)

Table I. Continued.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-133a; miR-133b	Esophageal squamous cell carcinoma	Inhibition of cell proliferation and cell invasion	FSCN1	Kano *et al* (188)
miR-135a	Prostate cancer	Inhibition of cell invasion and migration	ROCK1, ROCK2	Kroiss *et al* (189)
miR-137	Colorectal cancer	Reduction of invasiveness	FMNL2	Liang *et al* (190)
miR-143	Non-small cell lung cancer	Suppression of cell proliferation; inhibition of cell migration and invasion; induction of apoptosis	Limk1	Xia *et al* (191)
miR-145	Esophageal squamous cell carcinoma, colon carcinoma, gastric cancer, neuroblastoma	Inhibition of cell proliferation and cell invasion; reduced tumor proliferation and increased apoptosis; attenuation of gastric cancer cell migratory and invasive abilities *in vitro* and suppression of the metastatic cascade *in vivo*; inhibition of the invasion and metastasis of neuroblastoma cells	FSCN1, c-MYC, ERK5, N-cadherin, HIF-2α	Kano *et al* (188); Ibrahim *et al* (91); Gao *et al* (192); Zhang *et al* (193)
miR-146a/b	Prostate, breast cancer	Inhibition of cell invasion and migration	IRAK1, TRAF6, ROCK1	Bhaumik *et al* (194); Lin *et al* (195)
miR-148a	Liver, lung cancer	Inhibition of hepatoma cell migration *in vitro* and pulmonary metastatic colonization *in vivo*	MET/Snail signaling	Zhang *et al* (196)
miR-148b	Breast cancer	Inhibition of multiple steps of tumor progression via the regulation of invasion, resistance to anoikis, extravasation, lung metastasis, colonization and chemo-therapeutic response	ITGA5, ROCK1, PIK3CA/p110α, NRAS, CSF1	Cimino *et al* (197)
miR-149	Breast, lung cancer	Inhibition of basal-like breast cancer cell migration and invasion *in vitro*; impairment of lung colonization *in vivo*	Rap1a, Rap1b	Bischoff *et al* (198)
miR-181b	Chronic lymphocytic leukemia	Inhibition of disease progression	Mcl-1, Bcl-2	Visone *et al* (199)
miR-182	Glioblastoma	Inhibition of cell growth and cell differentiation	Bcl-2L12, c-MET, HIF2A	Kouri *et al* (200)
miR-193b	Breast cancer, pancreatic ductal adenocarcinoma	Alteration of ERα signaling, such as steroid synthesis and downregulation of the ERα receptor; negative regulation of long non-coding oncogenic RNA	AKR1C2, AKR1C1, YWHAZ (14-3-3 family protein), RNA MIR31HG	Leivonen *et al* (201); Yang *et al* (202)
miR-198	Hepatocellular carcinoma	Inhibition of migration and invasion	HGF/c-MET	Tan *et al* (203)
miR-204	Neuroblastoma, glioma	Stimulation of increased sensitivity to cisplatin treatment and promotion of cell survival; alteration of glioma progression, invasion and migration	TrkB	Bao *et al* (204); Xia *et al* (205)
miR-205	Human prostate cancer	Reduction of cell migration/ invasion through downregulation of protein kinase C epsilon	CHN1, ErbB3, E2F1, E2F5, ZEB2, PRKCE	Gandellini *et al* (206)

Table I. Continued.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-206	Breast cancer	Inhibition of cell invasion and migration	MET	Chen *et al* (207)
miR-214	Colorectal cancer, liver metastasis	Suppression of cell migration and invasion *in vitro*; inhibition of liver metastasis of colorectal cancer cells *in vivo*	FGFR1	Chen *et al* (208)
miR-218	Gastric cancer	Suppression of tumor metastases	ROBO1	Tie *et al* (209)
miR-296-5p	Prostate cancer	Reduction of growth invasion and progression	HMGA1	Wei *et al* (210)
miR-302	Breast cancer	Sensitization of radioresistant breast cancer cells to ionizing radiation	AKT1, RAD52	Liang *et al* (99)
miR-302b	Hepatocellular carcinoma	Suppression of cell proliferation	EGFR	Wang *et al* (211)
miR-335	Breast cancer	Inhibition of cell invasion, migration and metastasis	SOX4, PTPRN2, MERTK, TNC	Tavazoie *et al* (212); Hurst *et al* (213)
miR-383	Medulloblastoma	Control of cell growth	PRDX3	Li *et al* (214)
miR-449	Gastric cancer, non-small cell lung cancer	Inhibition of cell proliferation, inhibition of migration and invasion	GMNN, MET, CCNE2, SIRT1	Bou Kheir *et al* (215) Luo *et al* (216)
miR-493	Colon, lung cancer	Inhibition of the settlement of metastasized colon cancer cells in the liver; promotion of the death of colon cancer cells; suppression of tumor growth, invasion and metastasis in lungs	IGFR, E2F1, MKK7	Okamoto *et al* (217); Gu *et al* (218); Sakai *et al* (219)
miR-504	Hypopharyngeal squamous cell carcinoma	Inhibition of cancer cells proliferation	CDK6	Kikkawa *et al* (220)
miR-520c/373	Breast cancer	Inhibition of cell invasion *in vitro* and the cell intravasation *in vivo*	RELA, TGFBR2	Keklikoglou *et al* (221)
miR-545	Pancreatic ductal adenocarcinoma, lung cancer cells	Inhibition of cell growth and proliferation	RIG-1, CDK4	Song *et al* (222); Bowen *et al* (223)
miR-596	Oral squamous cell carcinoma (OSCC)	Growth inhibition	LGALS3BP	Endo *et al* (96)

potential of the systemic delivery of miR-200c to enhance radiosensitivity in lung cancer. The results obtained suggest that the antitumor effects of miR-200c result partially from its regulation of the oxidative stress response; they further suggested that miR-200c, in combination with radiation, may represent an effective therapeutic strategy in the future.

Recently, Wu *et al* (308) reported that the expression of miR-708-5p suppressed lung cancer invasion and metastasis *in vitro* and *in vivo*. In particular, it induces apoptosis and suppresses cell migration by inhibiting the cytoplasmic localization of p21, and also weakens the stem cell-like properties of lung cancer cells. In their study, they present the systemic delivery of the PEI/miR-708-5p complexes for miRNA replacement therapy in a mouse model of lung cancer, demonstrating an efficient antitumor activity with no side-effects.

5. Targeting oncomiRNAs

The effects of therapeutic molecules against miRNAs have been the object of very recent studies, in part summarized in Table V (309-316). Of course, the endpoint of the treatment of target cells with molecules against selected miRNAs is the alteration of miRNA-regulated genes. As a first example, Wagenaar *et al* (317) developed potent and specific single-stranded oligonucleotide inhibitors of miR-21 and used them to verify dependency on miR-21 in a panel of liver cancer cell lines. Treatment with anti-miR-21, but not with a mismatch control anti-miRNA, resulted in the significant derepression of direct targets of miR-21 and led to the loss of viability in the majority of HCC cell lines tested. The robust induction of caspase activity, apoptosis and necrosis was noted in the

Table II. miRNAs exhibiting oncogenic functions.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-10b	Human esophageal cancer cells, gastric carcinoma	Promotion of migration and invasion	KLF4	Tian *et al* (240); Wang *et al* (241)
miR-21	Breast, colon, pancreatic, lung, prostate, liver and stomach cancer, chronic lymphocytic leukemia; acute myeloid leukaemia, glioblastoma, neuroblastoma	Stimulation of cellular proliferation; action on mitochondrial apoptosis tumor-supressive pathways, resisting cell death	PTEN, TPM1, PDCD4, p63, RECK, p53, TGF-β	Chan *et al* (242); Zhu *et al* (230); Frankel *et al* (231); Volinia *et al* (233)
miR-23b	Renal cancer cells	Downregulation of POX (tumor suppressor), increase in HIF signaling	POX	Liu *et al* (243)
miR-27a	Prostate cancer	Increase in the expression of AR target genes and prostate cancer cell growth	PHB	Fletcher *et al* (244)
miR-100	Myeloid leukemia, glioma	Promotion of cell differentiation, survival and apoptosis	RBSP3, ATM	Ng *et al* (245); Zheng *et al* (246)
miR-125b	B-cell leukemia	Induction of cell differentiation and transformation	MAP3K11, ARID3B	Knackmuss *et al* (247)
miR-132 miR-212	Pancreatic adenocarcinoma (PDAC)	Stimulation of cell proliferation via the β2 adrenergic pathway	Rb1	Park *et al* 2011 (248)
miR-155	Lymphoma, leukemia, breast, colon, lung, pancreatic, thyroid brain cancer, diffuse large B-cell lymphoma (DLBCL)	Causes the constitutive activation of signal transducer and activator of transcription 3, sustaining proliferative signaling, resistance of cell death, activation invasion, migration and metastasis	SOCS1, RhoA, FOXO3a, VHL	Kong *et al* (249); Jiang *et al* (250); Czyzyk-Krzeska *et al* (251); Wang *et al* (252); Ling *et al* (253); Musilova *et al* (254)
miR-17	Neuroblastoma	Marked increase of *in vitro* and *in vivo* tumorigenesis	p21, BIM	Fontana *et al* (255)
miR-182	Melanoma	Promotion of melanoma metastases	MITF, FOXO3	Segura *et al* (256)
miR-214	Ovarian cancer	Stimulation of cell survival and cisplatin resistance	PTEN	Yang *et al* (257)
miR-221 miR-222	Atypical teratoid/rhabdoid tumors (ATRT), osteosarcoma, glioma, breast cancer, follicular thyroid carcinoma (FTC), digestive system carcinoma	Decrease of cell cycle inhibitor $p27^{Kip1}$, tumor development and progression by regulating proliferative signaling pathways, altering telomere and telomerase activity, avoiding cell death from tumor suppressors, autophagy and apoptosis, monitoring angiogenesis, supporting epithelial-mesenchymal transition, and even controlling cell-specific function within the microenvironment	$p27^{Kip1}$, PTEN, KIT, TRPS1, PUMA, PTPμ, FOXO3, PIK3R1, TIMP3, TIMP2, DDIT4, MDM2, ERα, SOCS3, OCS1, HDAC6, ANGPTL2, BBC3, BMF, RECK, PDLIM2, RelA, $p57^{Kip2}$	Zhang *et al* (258); Garofalo *et al* (259); Quintavalle *et al* (260); Chen *et al* (261); Matsuzaki *et al* (262)
miR-296	Brain tumors	Promotion of angiogenesis	HGS	Wurdinger *et al* (263)
miR-301	Breast cancer	Promotion of growth, proliferation, invasion and metastases	FOXF2, BBC3, PTEN	Shi *et al* (264)
miR-372 miR-373	Testicular tumors	Promotion of tumorigenesis in cooperation with RAS	LATS2	Voorhoeve *et al* (265)
miR-375	Gastric cancer	Promotion of carcinogenesis	JAK2, PDK1	Xu *et al* (266)

Table II. Continued.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-378	Breast carcinoma	Ehnancement of cell survival; reduction of caspase-3 activity; promotion of growth and angiogenesis	Sufu, Fus-1	Lee *et al* (267)
miR-519a	Hepatocellular carcinoma, breast cancer	Promotion of tumor growth, proliferation; inhibition of apoptosis; tamoxifen resistance	PTEN/PI3K/ AKT/FOXF2	Tu *et al* (268); Shao *et al* (269); Ward *et al* (270)
miR-675	Colorectal cancer	Overexpression of H19 (oncofetal non-coding RNA) in cancer tissues	RB	Tsang *et al* (271)
miR-1908	Glioblastoma	Promotion of anchorage independent growth *in vitro*, increasing of tumor forming potential *in vivo*	PTEN	Xia *et al* (238)

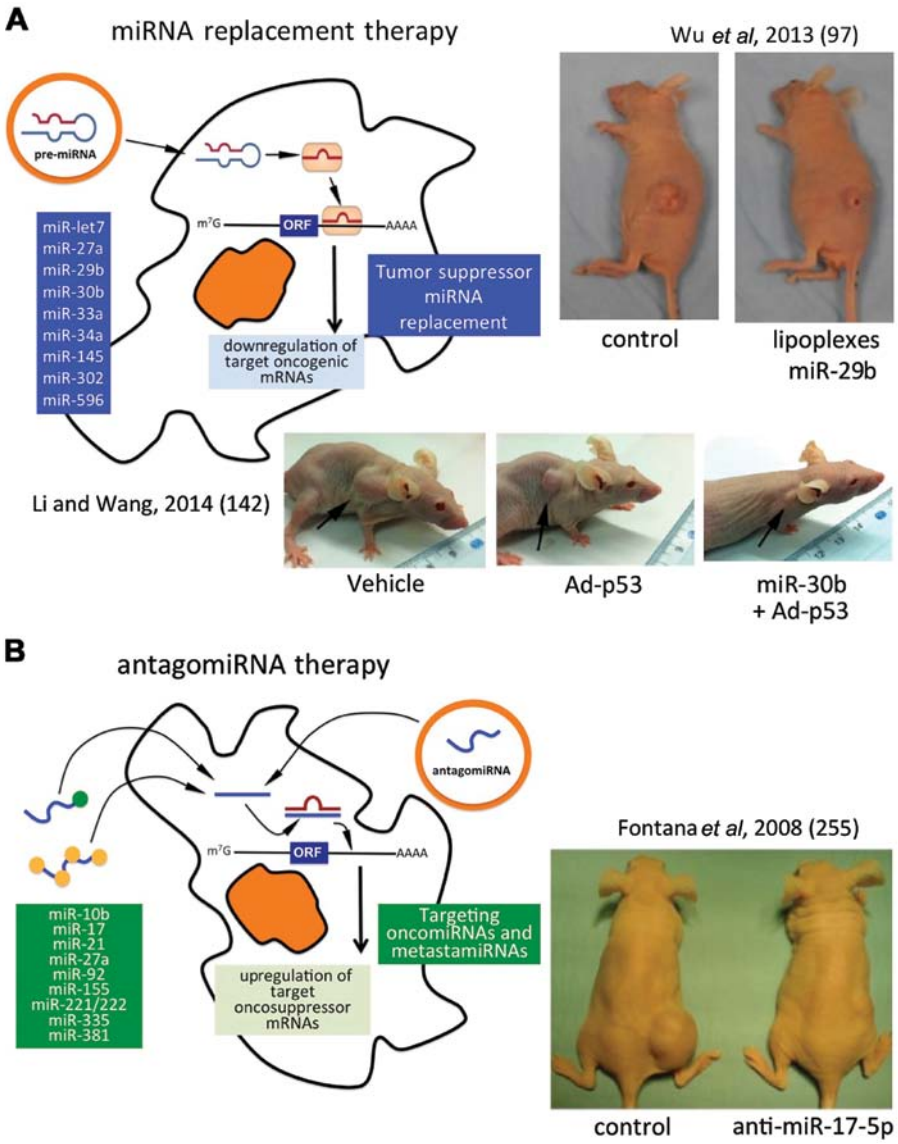

Figure 2. (A) miRNA replacement therapy: partial list of tumor suppressor miRNAs (in the blue box) and selected examples of the *in vivo* restoration of miR-29b (97) and of miR-30b (142), leading to the inhibition of tumor cell growth. (B) Targeting oncomiRNAs and metastamiRNAs with antagomiRNAs: partial list of onco/ metastamiRNAs and a selected example of the antitumor effects of antagomiR-17-5p (255).

Table III. miRNAs promoting metastasis.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-9	Breast, colon cancer	Promotion of breast cancer cell motility and invasiveness; enhancement of squamous cell carcinoma CSC expansion and metastasis	CDH1, LIFR, α-catenin	Ma *et al* (272); Chen *et al* (273); White *et al* (274)
miR-10b	Breast cancer, glioblastoma	Promotion of EMT, migration, invasion and metastasis	TP53, PAX6, NOTCH1, HOXD10	Ma *et al* (275); Lin *et al* (276)
miR-15b	Pancreatic cancer	Promotion of EMT	SMURF2	Zhang *et al* (277)
miR-19a/b	Gastric cancer	Facilitation of cell migration, invasion and metastasis	MXD1	Wu *et al* (278)
miR-20a	Cervical, gallbladder cancer	Facilitation of cancer cell proliferation and metastasis *in vitro* and increased tumor growth *in vivo*; induction of EMT	ATG7, TIMP2, Smad7	Chang *et al* (279); Zhao *et al* (280)
miR-21	Breast, lung, brain, cervical and colorectal cancer, melanoma	Drive to epithelial collective cell migration, invasion, cell metastasis and apoptosis; enhancement of colorectal cancer cell intravasion	TPM1, PDCD4, Maspin (SERPINB5), PTEN, PI3K, Sprouty, p53, cyclin D1, FOXO1, FBXO11, TIPE2,MSH2, hTERT, HIF1α, TIMP3, APAF1	Zhu *et al* (230); Dean *et al* (281); Peacock *et al* (282); Xu *et al* (283); Asangani *et al* (284); Hurst *et al* (213); Melnik *et al* (285)
miR-96	Prostate cancer	Bone metastasis, enhanced effects on cellular growth and invasiveness	TGF-β/mTOR signaling	Siu *et al* (237)
miR-105	Breast cancer	Destruction of the integrity of vascular endothelial barriers to promote metastasis	ZO-1	Zhou *et al* (286)
miR-122	Breast cancer	Promotion of metastatic colonization	PKM2,	Fong *et al* (287)
miR-135b	Lung cancer	Promotion of cell migration, invasion and metastasis	LATS2, TrCP, NDR2, LZTST1	Lin *et al* (288)
miR-181a	Breast cancer	Promotion of breast cancer metastasis	Bim/TGF-β	Taylor *et al* (289)
miR-182	Gallbladder, sarcoma, lung cancer	Promotion of metastasis, circulating tumor cells (CTC); regulation of intravasion	CADM1, RSU1, MTSS1, PAI1, TIMP1	Qiu *et al* (290); Sachdeva *et al* (239)
miR-183	Oesophageal carcinoma	Promotion of proliferation and invasion	PDCD4	Ren *et al* (291)
miR-200s	Breast, ovarian cancer	Activation of invasion and metastasis (but in other cases inhibition)	ZEB1, ZEB2, SIP1, Sec23a	Korpal *et al* (292); Korpal *et al* (293); Park *et al* (294); Gregory *et al* (295)
miR-214	Lung adenocarcinoma, melanoma	Promotion of migration, invasion and resistance to anoikis of melanoma cells *in vitro* and the extravasation and lung metastasis formation *in vivo*; promotion of EMT and metastasis	TFAP2C, Sufu	Penna *et al* (296); Penna *et al* (297); Long *et al* (298)
miR-296-3p	Prostate cancer	Promotion of metastasis	ICAM1	Liu *et al* (299)
miR-296-5p	Prostate cancer	Promotion of growth and invasion, metastatic progression, and persistence of cancer-initiating cells	Numbl (Klf4 signaling)	Vaira *et al* (300)

Table III. Continued.

MicroRNA	Disease	Biological effects	Target mRNA/ pathway	Authors/(Refs.)
miR-362-5p	Hepatocellular carcinoma	Promotion of cell proliferation, migration, invasion *in vitro*; and tumor growth and metastasis *in vivo*	CYLD	Ni *et al* (301)
miR-373	Breast cancer	Drives EMT and metastasis	TXNIP	Chen *et al* (302)
miR-520c	Fibrosarcoma, benign prostatic hyperplasia, glioblastoma	Promotion of migration and metastasis	MT1-MMP	Lu *et al* (303)

Table IV. miRNA replacement therapy of cancer: selected examples.

Tumor type	miRNA target	Modulated mRNA	Effects following miR treatement	Authors/(Refs.)
Lung cancer	miR-34a	Repression of c-Met, Bcl-2; partial repression of CDK4	Block of tumor growth	Wiggins *et al* (90)
Colon carcinoma	miR-33a	Pim-1	Reduced tumor proliferation	Ibrahim *et al* (91)
Colon carcinoma	miR-145	c-Myc and ERK5	Reduced tumor proliferation and increased apoptosis	Ibrahim *et al* (91)
Lung cancer	miR-let7	Negative regulation of the cell cycle oncogenes *RAS*, *MYC* and *HMGA2*	Reduction of tumor growth	Trang *et al* (92)
Acute leukemia	miR-27a	Bax and Bad	Inhibition of cell growth due, at least in part, to increased cellular apoptosis	Scheibner *et al* (94)
CML cells	miR-33a	Pim-1	Decelerated cell proliferation	Thomas *et al* (95)
Oral squamous cell carcinoma (OSCC)	miR-596	LGALS3BP	Growth inhibition	Endo *et al* (96)
Non-small cell lung adenocarcinomas, A549 cells	miR-29b	CDK6, DNMT3B, MCL-1	Inhibition of tumorigenicity *in vivo*	Wu *et al* (97)
Acute myeloid leukemia	miR-29b	Downregulation of DNMTs, CDK6, SP1, KIT and FLT3	Decreased AML cell growth and impairement of colony formation; longer survival of treated mice; improvement of antileukemic activity of decitabine	Huang *et al* (98)
Laryngeal carcinoma	miR-30b	p53 via MDM2	Antitumor and pro-apoptotic effect *in vivo* and *in vitro*	Li and Wang (142)
Breast cancer	miR-302	AKT1 and RAD52	Sensitized radioresistant breast cancer cells to ionizing radiation	Liang *et al* (99)

anti-miR-21-treated HCC cells. Furthermore, the ablation of miR-21 activity resulted in the inhibition of HCC cell migration and in the suppression of clonogenic growth (317).

In another study, using PNAs as anti-miRNA molecules, Fabani *et al* (318) targeted miR-155, demonstrating the deregulation of mRNA Bat5, Sfp1 and Jarid2. In our laboratory, Brognara *et al* analyzed the effects of PNAs targeting miR-221 on breast cancer cells (319). In order to maximize uptake in target cells, a polyarginine-peptide (R8) was conjugated, generating an anti-miR-221 PNA displaying very high affinity for RNA and efficient uptake within target cells without the need for transfection reagents. Targeting miR-221 with this PNA molecule resulted in i) a specific decrease in the hybridization levels of miR-221 measured by RT-qPCR, ii) the upregulation of

Table V. AntagomiR-based miRNA targeting therapy of cancer: selected examples.

Cells/tissues	miRNA target	Modulated mRNA	Effects following antagomiR treatment	Authors/(Refs.)
Neuroblastoma	miR-17	p21, BIM	Strongly increase of *in vitro* and *in vivo* tumorigenesis	Fontana *et al* (255)
Human glioblastoma	miR-27a	FOXO3a	Suppression of U87 growth *in vitro* and *in vivo*	Ge *et al* (309)
Malignat astrocytoma cells	miR-335	Daam1	Growth arrest, cell apoptosis, invasion repression and marked regression of astrocytoma xenografts	Shu *et al* (310)
Cutaneous squamous cell carcinoma (SCC)	miR-155	CDC73	Decreased cell viability, increased apoptosis, and marked regression of xenografts in nude mice	Rather *et al* (311)
Neuroblastoma	miR-92	DKK3	Increases release of the tumor suppressor Dickkopf-3 (DKK3), a secreted protein of the DKK family of Wnt regulators	Haug *et al* (312)
Glioma	miR-381	LRRC4	Decreased cell proliferation and tumor growth	Tang *et al* (313)
Breast cancer	miR-10b	Hoxd10	Suppression of formation of lung metastases	Ma *et al* (314)
Prostate cancer	miR-221/miR-222	p27	Reduction of tumor growth	Mercatelli *et al* (315)
Pancreatic cancer	miR-221/miR-21	SOCS6, SMAD7, CDK6, KLF12, MAPK10	Modulation of tumorigenesis, metastasis, and chemotherapy resistance in stem-like cells	Zhao *et al* (316)

$p27^{Kip1}$ mRNA and protein expression, measured by RT-qPCR and western blot analysis, respectively. As regards the *in vivo* effects of anti-miRNA therapy, Yan *et al* (320) addressed the potential effects of PNA-anti-miR-21 *in vivo* on the growth of breast cancer cells. In their experiments, MCF-7 cells treated with PNA-anti-miR-21 or PNA-control were subcutaneously injected into female nude mice and detectable tumor masses were observed in few mice in the MCF/PNA-anti-miR-21 group, while much larger tumors were detected in all mice in the MCF/PNA-control group. Both tumor weight and number showed that MCF/PNA-control cells formed larger tumors more rapidly than MCF/PNA-anti-miR-21 cells in nude mice. As a final example, Cheng *et al* (57) demonstrated that the PNA anti-miRs with a peptide with a low pH-induced transmembrane structure (pHLIP) target the tumor microenvironment, transport anti-miRs across plasma membranes under acidic conditions, such as those found in solid tumors and effectively inhibit the miR-155 oncomiR in a mouse model of lymphoma.

6. MicroRNAs and epithelial-mesenchymal transition

EMT is a powerful process in tumor invasion, metastasis and tumorigenesis, and describes the molecular reprogramming and phenotypic changes that are characterized by a transition from polarized immotile epithelial cells to motile mesenchymal cells (Fig. 3). This process is characterized by the loss of polarity and cell-cell contacts by the differentiated epithelial cells, with deep alterations occurring at the level of tight junctions and desmosomes. The breach of the basement membrane is a following step, leading to the invasion of blood and/or lymphatic vessels by these mesenchymal differentiated cancer cells, which at the end of the process, causes migration, often accompanied by drug resistance (Fig. 3). It is now well-known that several miRNAs are important regulators of EMT. Some of these are miR-7, miR-17/20, miR-22, miR-30, miR-200 and its family members. Most of these miRNAs potentiate EMT, while some well-characterized miRNAs play a suppressive role in EMT. For instance, the metastasis suppressor role of the miR-200 members is strongly associated with the inhibition of EMT. This is well described in the published review by Zhang and Ma (321), and in the studies by Zaravinos *et al* (322) and Kiesslich *et al* (323), showing the most recent advances regarding the influence of miRNAs in EMT and the regulatory effects they exert on major signaling pathways in various types of cancer (Fig. 3). In Caski cervical cancer cells, the oncomiR-155 acts as a tumor suppressor and suppresses EGF-induced EMT, decreasing migration/invasion capacities, inhibiting cell proliferation and enhancing the chemosensitivity to DDP in humans (324). Chang *et al* (279) demonstrated that the overexpression of miR-20a in gallbladder carcinoma cells induced EMT and promoted metastasis via the direct inhibition of Smad7, correlating this miRNA with local invasion, distant metastasis and a poor prognosis in patients with gallbladder carcinoma.

In the ovarian surface epithelium, EMT is considered the key regulator of the post-ovulatory repair process and it can be triggered by a range of environmental stimuli. The aberrant expression of the miR-200 family (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) in ovarian cancer, and its involvement in the initiation and progression of ovarian cancer have been well demonstrated. The miR-200 family members seem to be strongly associated with EMT and to have a

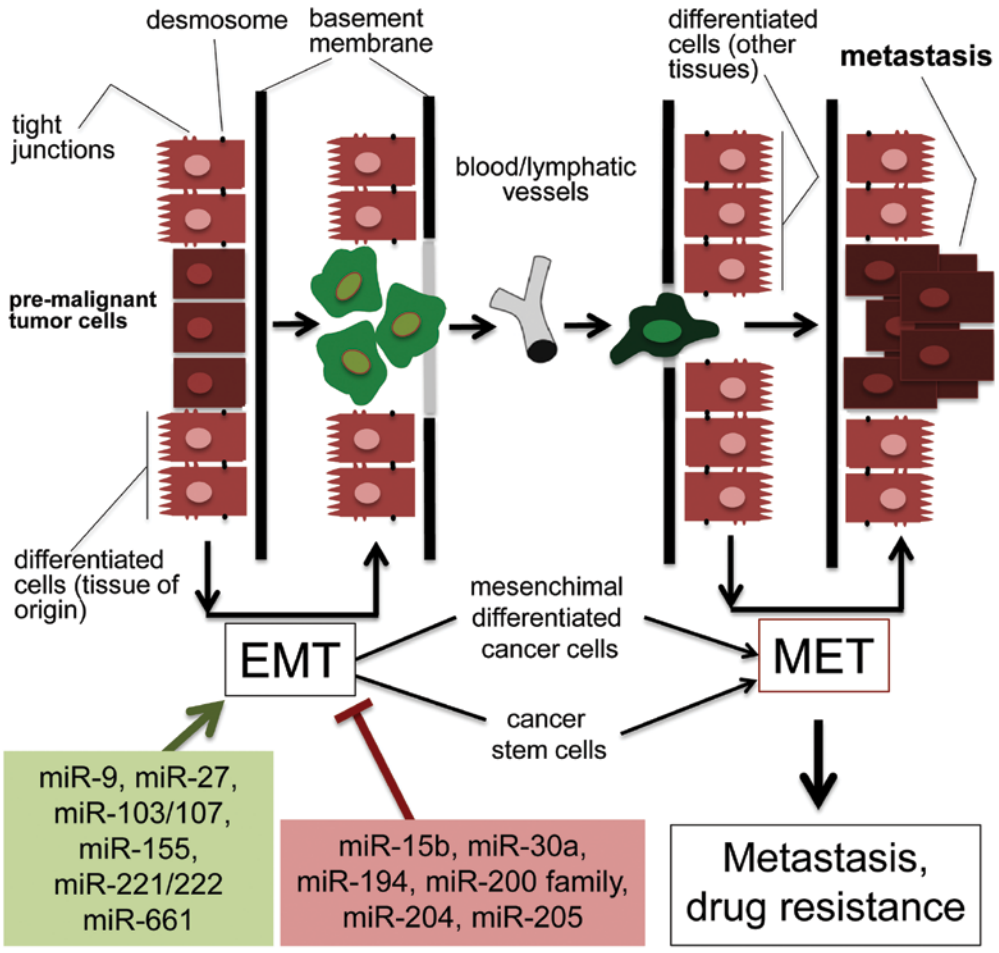

Figure 3. Epithelial-mesenchymal transition (EMT), a powerful process leading to tumor invasion and metastasis. Examples of EMT-promoting miRNAs are reported in the green box, while examples of EMT-interfering miRNAs are reported in the pink box. Modified from Kiesslich *et al* (323).

metastasis suppressor role. miRNA signatures can accurately distinguish ovarian cancer from the normal ovary and can be used as diagnostic tools to predict the clinical response to chemotherapy. Recent evidence suggests a growing list of novel miRNAs (miR-187, miR-34a, miR-506, miRNA-138, miR-30c, miR-30d, miR-30e-3p, miR-370 and miR-106a, among others) that are also implicated in ovarian cancer-associated EMT, either enhancing or suppressing it. MicroRNA-based gene therapy provides a prospective antitumor approach for integrated cancer therapy (325).

As regards the molecular targets of EMT-regulating miRNAs, several are known and validated. Among these, transcription factors play a very important role. For instance, Gao *et al* (326) identified SOX2 as a key player in EMT, by examining the effects of its overexpression. They demonstrated that SOX2-overexpressing Eca-109 cells exhibited an enhanced cell migration/invasion capacity. Moreover, these cells exhibited characteristics of EMT, that is, a significantly suppressed expression of the epithelial cell marker with a concomitant enhancement in the expression of mesenchymal markers. An increased expression of Slug in SOX2-overexpressing cells suggested the involvement of this transcription factor in SOX2-regulated metastasis. Finally, the expression levels of STAT3/HIF-1α were found to be upregulated in SOX2-expressing cells, and the blockade of these transcription factors resulted in the inhibition of Slug expression at both the protein and mRNA level.

Of interest, is also the finding that miR-221/222, which are involved in EMT as positive regulators, can be transcriptionally controlled by Slug. This was demonstrated by Lambertini *et al* (327), who showed that Slug silencing significantly decreased the level of miR-221, strongly suggesting that miR-221 is a Slug target gene. This was further confirmed by the characterization of a specific region of the miR-221 promoter that is transcriptionally active and is bound by the transcription factor Slug *in vivo*.

On the other hand, various miRNAs have been reported to directly target EMT-promoting transcription factors. For instance Qiu *et al* (328) found that miR-139-5p functions as a suppressor of EMT in HCC and metastasis by targeting ZEB1 and ZEB2, and that it may be a therapeutic target for metastatic HCC. In conclusion, miRNAs targeting and miRNA mimicking strategies are both expected to be suitable for the control of EMT.

7. MicroRNAs and neoangiogenesis

A very important step in tumor dissemination and metastasis is neoangiogenesis. This is a very complex process in which several proteins and protein networks participate, for instance

interleukin (IL)-8, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoietins and matrix metalloproteinases (MMPs). As far as the expression of the IL-8 gene is concerned, the increase in IL-8 gene expression from the healthy brain to low-grade glioma (LGG) can be explained by alterations in the regulatory networks associated with IL-8 gene transcription. Among these, the nuclear factor-κB (NF-κB) network should be proposed, since i) NF-κB is one of the major transcription factors involved in IL-8 gene regulation (329); ii) NF-κB is a marker of glioma onset and progression (330-333); iii) miR-16 inhibits glioma cell growth through the suppression of the NF-κB signaling pathway (334). In addition to transcription factors, miRNAs can directly modulate pro-angiogenic factors. For instance, the increased IL-8 gene expression in high-grade glioma (HGG; with respect to LGG) may be associated with decrease of its inhibitory miRNA, miR-93, at least in a subset of HGG patients. The decrease in miR-93 expression in these HGG patients, in addition to IL-8, may lead to the post-transcriptional upregulation of VEGF, monocyte chemoattractant protein-1 (MCP-1) and platelet-derived growth factor (PDGF)-bb, well recognized markers of the late tumor stages of gliomas (335-337). However, it should be mentioned that HGG samples are highly heterogeneous with respect to miR-93 levels, suggesting the involvement of multiple regulatory pathways in controlling the level of IL-8 gene expression.

8. Selected examples of miRNA therapeutics: mimicking miR-124

One of the better described examples of tumor suppressor miRNAs is miR-124. This miRNA has been found to play a significant role in several types of cancer (168-173,338). Specifically, miR-124 expression is reportedly downregulated in the cells and tissues of esophageal cancer (339), breast cancer (340), renal cell carcinoma (341) and CRC (172). Accordingly, the ectopic expression of miR-124 by target tumor cells inhibits tumor-related parameters in experimental model systems mimicking prostate cancer, medulloblastoma, hepatocellular carcinoma, gastric cancer, glioma, osteosarcoma and CRC.

For instance, Taniguchi *et al* (164) recently demonstrated that the ectopic expression of miR-124 induced apoptosis and autophagy in colon cancer cells. In addition, miR-124 was demonstrated to target polypyrimidine tract-binding protein 1 (PTB1), which is a splicer of pyruvate kinase muscles 1 and 2 (PKM1 and PKM2), and to induce the switching of PKM isoform expression from PKM2 to PKM1 (164). In addition to this study, Lu *et al* (342) demonstrated that miR-124a expression was downregulated in human glioma tissues, and that its expression level negatively correlated with the pathological grade of the glioma. The restoration of miR-124a inhibited glioma cell proliferation and invasion *in vitro*.

Furthermore, they found that miR-124a directly targeted and suppressed IQ motif containing GTPase activating protein 1 (IQGAP1), a well-known regulator of actin dynamics and cell motility (342). Taken together all these data clearly demonstrate that miR-124a is an important tumor suppressor miRNA which is downregulated in cancer cells; accordingly antitumor effects can be achieved following the administration of miR-124, pre-miR-124 or a variety of miR-124 mimics to cancer cells.

Finally, the translational relevance of the role of miR-124 in antitumor drug sensitivity is suggested by the finding that the increased miR-124 expression correlates with an improved breast cancer prognosis, specifically in patients receiving chemotherapy. This finding suggests that miR-124 may potentially be used as a therapeutic agent to improve the efficacy of chemotherapy, including that based on DNA-damaging agents via ATM interactor (ATMIN)- and poly(ADP-ribose) polymerase 1 (PARP1)-mediated mechanisms (343).

9. Selected examples of miRNA therapeutics: mimicking miR-93

A second example of possible miRNA replacement therapy is based on the inhibition of IL-8 and VEGF by the transfection of tumor target cells with pre-miR-93. This was performed in human glioma cell lines (U251 and T98G), as well as on the SK-N-AS neuroblastoma cell line.

The first conclusion of this research activity is that the miRNA, miR-93, is involved in the control of the expression of the IL-8 gene in the glioma U251 and in the neuroblastoma SK-N-AS cell lines (344,345). The effects of these treatments were analyzed by RT-qPCR (looking at the IL-8 mRNA content) or by Bio-plex analysis (looking at IL-8 protein secretion). In addition, Fabbri *et al* (344) found that the transfection of target cells with pre-miR-93 led to the downregulation of VEGF (see the results depicted in Fig. 4A), suggesting that, as shown in Fig. 4B, miR-93 has effects on the growth of gliomas [by interfering with growth factors, including PDGF, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte-colony stimulating factor(G-CSF)], as well as on neoangiogenesis.

10. Selected examples of anti-miRNA therapeutics: targeting miR-221/222

Gliomas, as other tumors, express miR-221 at high levels, promoting malignant progression through activation of the Akt pathway and the inhibition of $p27^{Kip1}$ (346-349). In addition miR-221 mediates the downregulation of other genes, such as PUMA (258), intercellular adhesion molecule 1 (ICAM-1) (350), TIMP metallopeptidase inhibitor 3 (TIMP3) (351) and phosphatase and tensin homolog (PTEN) (352), and may thus be associated with cancer onset and progression (353). Therefore, miR-221 appears to be a specific target for the treatment of gliomas (354,355). Zhang *et al* (354) reported that the co-suppression of the miR-221/222 cluster suppressed human glioma cell growth by affecting $p27^{Kip1}$ expression *in vitro* and *in vivo*. In our own laboratory, we have also examined the effects of a PNA against miR-221 and showed that it is able to induce a sharp decrease in miR-221 biological activity. The employed PNA carryed an Arg(8) peptide to facilitate PNA uptake by target cells. Two studies were published on this specific issue. In the first study by Brognara *et al* (319), we demonstrated that targeting miR-221 induced a sharp increase in the expression of the miR-221 target $p27^{Kip1}$ mRNA in a breast cancer cell line (319). In a more recent study of ours, Brognara *et al* (56)

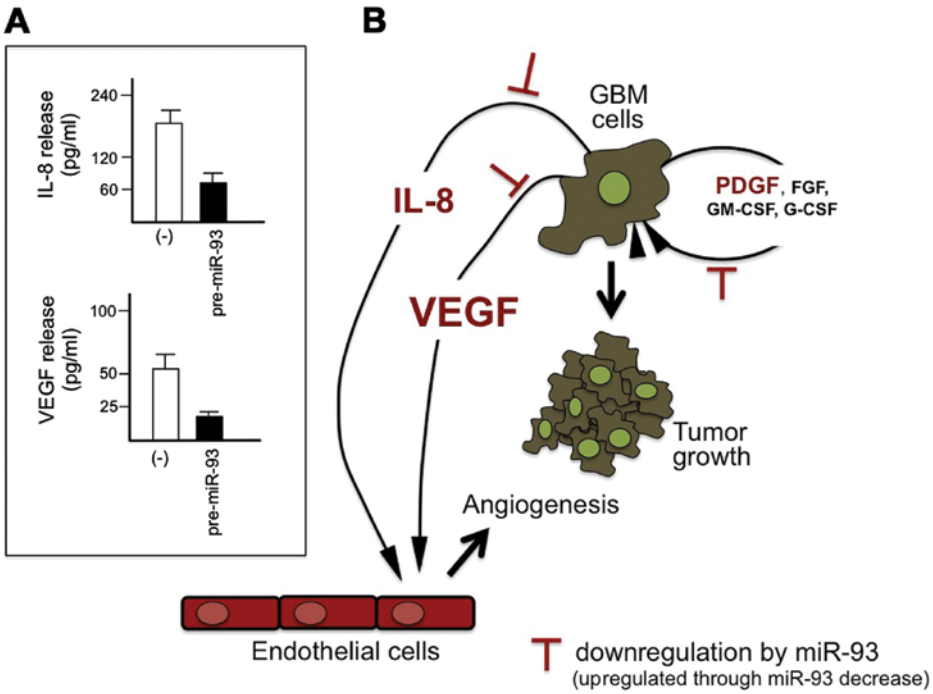

Figure 4. (A) Transfection of U251 glioma cells with pre-miR-93 leads to the downregulation of interleukin-8 (IL-8) (upper panel) and vascular endothelial growth factor (VEGF; lower panel) protein expression. (B) Scheme outlining the effects of pre-miR-93 on neoangiogenesis and tumor growth in gliomas. Modified from Fabbri *et al* (344).

demonstrated that the PNA against miR-221 can be internalized by glioma cells when linked to a Arg(8) tail (R8), leading to the inhibition of miR-221 functions, associated with the increased expression of $p27^{Kipl}$ in U251 and T98G cells. In addition, the expression of another miR-221 target gene, TIMP3, was upregulated following treatment of the T98G cells with R8-PNA-a221. These data support the concept that targeting miR-221 with antagomiR molecules may provide novel options for developing protocols for the treatment of gliomas. This is supported by the finding that the treatment of all the glioma cells lines with R8-PNA-a221 induced the activation of the early apoptotic pathway (56).

11. Combined treatments: targeting multiple miRNAs

Several tumors express upregulated levels of several miRNAs, suggesting that a possible limit to anti-mRNA therapeutics may be the requirement of the co-targeting of several miRNAs to obtain the programmed biological effects. Moreover, an important anti-miRNA strategy may be associated with the obvious need for the co-targeting of different miRNAs belonging to the same miRNA family.

miRNA-replacement therapy. Yang *et al* (356) found that the co-transfection of miR-137/197 resulted in a reduction in myeloid cell leukemia 1 (MCL-1) protein expression, as well as in the alteration of the expression of apoptosis-related genes, the induction of apoptosis, and in the inhibition of the viability, colony-forming ability and migration ability of multiple myeloma cells. MCL-1 was further validated as a direct target of miR-137/197. Conversely, the overexpression of MCL-1 partially reversed the effects of miR-137/197. Importantly, the *in vivo* lentiviral-mediated or intratumor delivery of miR-137/197 induced the regression of tumors in murine xenograft models of multiple myeloma (356).

Anti-miRNA therapy. The co-treatment of target cells with antagomiR molecules selective for different miRNAs has been recently described. For instance, Lee *et al* (357) investigated the role of miRNAs targeting runt related transcription factor 3 (RUNX3) in early tumorigenesis. Under hypoxic conditions, miR-130a and miR-495 are upregulated and target RUNX3 by binding to its 3'-UTR in gastric cancer cells. Using matrigel plug assay, they found that antagomiRs specific for miR-130a and miR-495 significantly reduced angiogenesis *in vivo* and hypothesized that the co-targeting of miR-130a and miR-495 may prove to be a potential therapeutic strategy with which to recover RUNX3 expression under hypoxic conditions and in early tumorigenesis (357).

In a recent study, Brognara *et al* (358) treated glioma cell lines with a combined administration of antagomiR-PNAs targeting miR-221 and miR-222. In fact, the same site recognized by miR-221 in the 3'UTR of target mRNAs can be also identified by miR-222, as suggested by predicted molecular interactions using PUMA 3'UTR as a model system. Therefore, the targeting of miR-221 with antagomiRs may not be sufficient to achieve the complete suppression of miR-221 biological activity due to the presence of miR-222 in target cells. Since miR-221 and miR-222 belong to the same transcriptional unit and are, as expected, co-expressed in tumor cell lines (U251, U373 and T98G), Zhang *et al* (354) determined whether the co-administration of antagomiRs recognizing miR-221 and miR-222 would lead to a more efficient inhibitory activity on miR-221/222 dependent functions. The results obtained

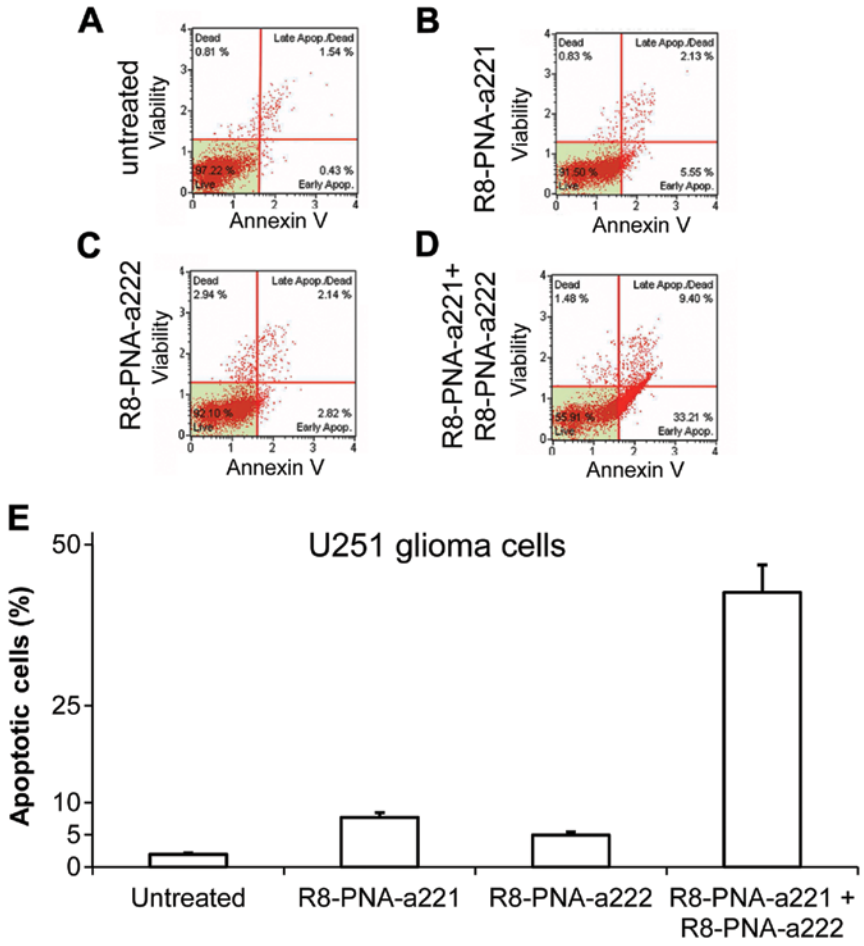

Figure 5. (A-D) Co-administration of R8-conjugated PNAs against miR-221 (R8-PNA-a221) and miR-222 (R8-PNA-a222) exhibits increased effects on the apoptosis of treated U251 glioma cells. Human glioma U251 cells were cultured (A) without, or (B) in the presence of 4 μM R8-PNA-a221, (C) 4 μM R8-PNA-a222 or (D) 2 μM R8-PNA-a221 plus 2 μM R8-PNA-a222. After 48 h of treatment, an analysis of the induction of apoptosis was conducted using the Annexin V assay and the Muse instrument, as described in detail in the study by Brognara *et al* (56). (E) Quantitative results derived by the data shown in (A-D). The most potent apoptosis-inducing effects were observed with the co-treatment of the U251 cells with R8-PNA-a221 and R8-PNA-a222. Modified from Brognara *et al* (358).

demonstrated that the co-suppression of miR-221/222 directly resulted in the upregulation of $p27^{Kip1}$ in the tested cells and in the inhibtion of cell growth by reducing a G1 to S shift in the cell cycle. Consistently, the knockdown of miR-221/222 through antisense 2'-OME-oligonucleotides increased $p27^{Kip1}$ expression in mice with U251 glioma subcutaneous tumors and markedly reduced tumor growth *in vivo* through the upregulation of $p27^{Kip1}$ (354).

In our own laboratory, we have approached the same issue using PNAs. We have previously reported that a PNA targeting miR-221 can be internalized by glioma cells and exert biological effects on miR-221-dependent functions when it is linked to an octaarginine tail (R8) (56). The major results of the more recent study by Brognara *et al* (358) are the following: i) R8-conjugated PNAs against miR-221 (R8-PNA-a221) and miR-222 (R8-PNA-a222) exhibit selective biological activity on miR-221 and miR-222; ii) when R8-PNA-a221 and R8-PNA-a222 are singularly administered to glioma cells, the specific inhibition of hybridization to miR-221 and miR-222 is obtained following RT-qPCR analysis; iii) both R8-PNA-a221 and R8-PNA-a222 induce the apoptosis of U251, U373 and T98G glioma cells. Finally, the co-administration of R8-PNA-a221 and R8-PNA-a222 was associated with the most prominent effects of this treatment in inducing apoptosis (see the representative experimental results shown in Fig. 5) (358).

12. Combined treatments: co-administration of antitumor drugs and miRNA therapeutic agents

One of the most interesting results obtained to date using miRNA therapeutics is the formal demonstration that, when used in combination with antitumor drugs, satisfactory therapeutic effects may be achieved (359). This has been demonstrated using both miRNA mimicking approaches, as well as anti-miRNA molecules.

miRNA replacement therapy. Gao *et al* (360), demonstrated that clear-cell renal cell carcinoma is a tumor type which is highly resistant to treatment and that the miR-200 family was involved in the process of mesenchymal-epithelial transition (MET) during renal development. In their study, evidence was provided to indicate that miR-200c sensitizes ccRCC cells to sorafenib or imatinib to inhibit cell proliferation. The combined application of chemotherapeutic drugs and

miR-200c may enhance the efficacy of therapy by promoting both apoptosis and autophagy (360). Another study demonstrating the enhanced effects of the combination of miRNA replacement therapy with antitumor drugs was published by Huang *et al* (98) with a novel transferrin-conjugated nanoparticle delivery system for synthetic miR-29b (Tf-NP-miR-29b), designed for intervention in the treatment of acute myeloid leukemia (AML). The antileukemic activity of Tf-NP-miR-29b was evaluated by measuring cell proliferation and colony-forming ability *in vitro,* as well as *in vivo* using a leukemia mouse model system. Tf-NP-miR-29b treatment significantly downregulated miR-29b targets, such as DNA methyltransferases (DNMTs), CDK6, specificity protein 1 (SP1), KIT and Fms-related tyrosine kinase 3 (FLT3), decreased AML cell growth and impaired colony formation. Mice engrafted with AML cells and then treated with Tf-NP-miR-29b had a significantly longer survival compared with the mice treated with Tf-NP-scramble or free miR-29b. Furthermore, priming AML cells with Tf-NP-miR-29b before treatment with decitabine resulted in a marked decrease in cell viability *in vitro* and enhanced the antileukemic activity compared to treatment with decitabine alone *in vivo*, suggesting that miRNA replacement therapy based on the delivery of miR-29b can be proposed for AML therapy also in combination with antitumor drugs.

Moreover, the study by Pogribny *et al* (361) reported that miR-7 expression directly targeted and significantly inhibited multidrug resistance-associated protein 1 (MPR1), which enhanced sensitivity to cisplatin in cisplatin-resistant breast cancer. Furthermore, an *in vitro* study by Suto *et al* (362) demonstrated that miR-7 overexpression enhanced sensitivity to cetuximab and suppressed cell proliferation after treatment with cetuximab in HCT-116 and SW480 cetuximab-resistant CRC cells. Additionally, miR-7 was found to enhance the sensitivity of non-small cell lung cancer (NSCLC) to paclitaxel (PTX) by promoting PTX-induced apoptosis (363). Another recent study demonstrated that the restoration of miR-143 and miR-145 expression in mutant KRAS (HCT116 and SW480) and wild-type KRAS (SW48) colon cancer cells re-sensitized the colon cancer cells to cetuximab by promoting cetuximab-mediated antibody-dependent cellular cytotoxicity (ADCC) to induce cell death (364).

In our own laboratory, we further analyzed the possible co-admistration of temozolomide (TMZ) and the tumor suppressor pre-miR-124. This was investigated in one neuroblastoma and two glioma cell lines. For miRNA replacement, we employed transfection with pre-miR-124, since miR-124 is a powerful tumor suppressor pro-apoptotic miRNA. In order to demonstrate the activity of the combined treatment, the antiproliferative and pro-apoptotic effects were analyzed. This set of data confirm that miRNA therapeutics can be successfully combined with chemical treatments to obtain greater effects with low doses of reagents. In conclusion, our data showed that, in addition to the combinations between antitumor drugs and antagomiR-based protocols, interesting results can be obtained by the combination of drugs with miRNA replacement agents (Fabbri *et al*, unpublished data).

Anti-miRNA therapy. As regards the use of anti-miRNA molecules, Costa *et al* (365) developed an efficient delivery system for anti-miR-21 oligonucleotides, showing preferential accumulation within brain tumors and efficient miR-21 silencing, which resulted in increased mRNA and protein levels of the miR-21 target RhoB. Decreased tumor cell proliferation and tumor size, as well as enhanced apoptosis and, to a lesser extent, the improvement of animal survival, were observed in glioblastoma tumor-bearing mice upon the systemic delivery of targeted nanoparticle-formulated anti-miR-21 oligonucleotides and exposure to the tyrosine kinase inhibitor, sunitinib (365). Although further studies are warranted to demonstrate a therapeutic benefit in the clinical context, these findings suggest that miRNA modulation by targeted nanoparticles combined with anti-angiogenic chemotherapy may hold promise as an attractive therapeutic approach. Other studies have reported that the downregulation of miR-21 can induce cell apoptosis and reverse drug resistance in cancer treatments; a synergistic antiproliferative and pro-apoptotic activity was obtained using combined treatment, based on anti-miR-21 molecules and temozolomide (366) or doxorubicin (367) in human glioma cell lines. In our own laboratory, we determined whether the treatment of T98G cells with R8-PNA-a221 or R8-PNA-a222 reverses the resistance of the cells to apoptosis induced by TMZ and found that when R8-PNA-a221 and R8-PNA-a222 are co-administered, the reversion of TMZ resistance was much more efficient as opposed to single treatments (358).

A recent study reported the co-delivery of antagomiR-10b and PTX by a liposomal delivery and showed that it efficiently inhibited tumor growth and reduced the incidence of lung metastasis. In fact, antagomiR-10b impeded the migration of 4 T1 cells *in vitro*, silencing miR-10b and upregulating Hoxd10 both *in vitro* and *in vivo*, while PTX elicited potent tumor cell inhibitory effects (368). The same antitumor efficacy and delivery to the tumor site may be achieved by the dual loading of miR-218 mimic (bio-drug) and temozolomide (chemo-drug) using a new delivery nanogel system approach (369).

13. Combining miRNA replacement strategies with anti-miRNAs and siRNA molecules

Xue *et al* (370) verified the biological activity of novel lung-targeting nanoparticles capable of delivering miRNA mimics and siRNAs to lung adenocarcinoma cells *in vitro* and to tumors in a genetically engineered mouse model of lung cancer based on the activation of oncogenic Kirsten rat sarcoma viral oncogene homolog (Kras) and the loss of p53 function. The therapeutic delivery of miR-34a, a p53-regulated tumor suppressor miRNA, restored the miR-34a levels in lung tumors, specifically downregulated miR-34a target genes, and attenuated tumor growth. The delivery of siRNAs targeting Kras reduced Kras gene expression and MAPK signaling, increased apoptosis and inhibited tumor growth. The combination of miR-34a and siRNA targeting Kras improved the therapeutic responses as compared to those observed with either small RNA alone, leading to tumor regression. Furthermore, nanoparticle-mediated small RNA delivery plus conventional, cisplatin-based chemotherapy prolonged survival in this model compared to chemotherapy alone. These findings demonstrate that RNA combination therapy is possible in a model of lung cancer and provide preclinical support for the use of small RNA therapies in patients who have cancer (370). A second

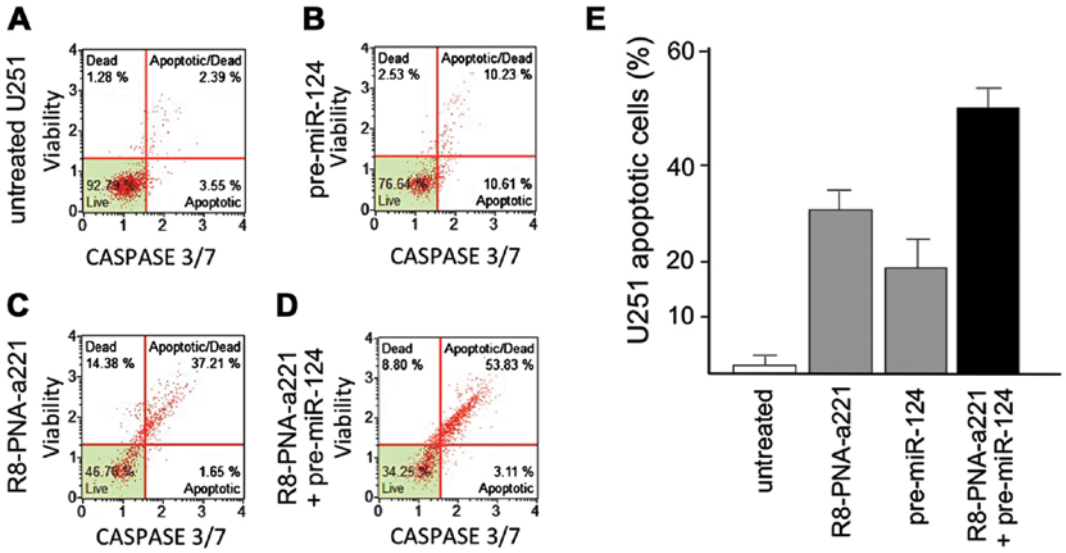

Figure 6. Treatment of U251 glioma cells with (B) 10 nM pre-miR-124, (C) 4 μM R8-PNA-a221 targeting miR-221 or (D) a combined administration of 10 nM pre-miR-124 and 4 μM R8-PNA-a221. (A) Control untreated cells are shown. After 48 h of treatment, the effects on apoptosis were analyzed by the caspase-3/7 assay and the Muse instrument. (E) Quantitative results derived by the data shown in (A-D). The most potent apoptosis-inducing effects were observed with the co-treatment of U251 cells with R8-PNA-a221 and pre-miR-124 (Fabbri *et al*, unpublished data).

example is that published by Nishimura *et al* (371) who first demonstrated that the siRNA-mediated silencing of EphA2, an ovarian cancer oncogene, resulted in the reduction of tumor growth. Second, they presented evidence that the additional inhibition of EphA2 by an miRNA further 'boosts' its antitumor effects. They identified miR-520d-3p as a tumor suppressor upstream of EphA2. The restoration of miR-520d-3p prominently decreased EphA2 protein levels, and suppressed tumor growth and migration/invasion both *in vitro* and *in vivo*. The dual inhibition of EphA2 *in vivo* using nanoliposomes loaded with miR-520d-3p and EphA2 siRNA exhibited synergistic antitumor efficiency and greater therapeutic efficacy than either monotherapy alone. These data emphasize the feasibility of combined miRNA-siRNA therapy, and will have broad implications for innovative gene silencing therapies for cancer and other diseases.

A further example in this very exciting field of investigation was reported by Hu *et al* (372), studying Bcl-2, a prominent member of the Bcl-2 family of proteins that regulate the induction of apoptosis. They investigated the effect of Bcl-2 siRNAs combined with miR-15a oligonucleotides on the growth of Raji cells. Following transfection of these combined reagents, the protein and mRNA levels of Bcl-2 were markedly decreased. The growth of the cells was significantly inhibited compared with the cells transfected with Bcl-2 siRNA or miR-15a alone and the apoptotic rate significantly increased. These results suggest that the combination of Bcl-2 siRNA and miR-15a oligonucleotides increases the apoptosis of Raji cells, and strongly support the concept that the combination of Bcl-2 siRNA and miR-15a may be a useful approach in the treatment of lymphoma.

Finally, an example of possible combined treatment is shown in Fig. 6, which indicates that the co-treatment of U251 cells with PNAs targeting miR-221 or miR-222 in the presence of pre-miR-124 transfection leads to a much higher level of apoptosis as opposed to singularly administered reagents (Fabbri *et al*, unpublished data).

14. Conclusion

MicroRNA therapeutics in cancer are based on targeting or mimicking miRNAs involved in cancer onset, progression, angiogenesis, EMT and metastasis. This strategy has been proposed several years ago and is based on the well-recognized fact that miRNAs play a key role in the post-transcriptional control of gene expression by the sequence-selective targeting of mRNAs and are key players in several biological functions and pathological processes, including cancer. In this respect, several studies have conclusively demonstrated that miRNAs are deeply involved in tumor onset and progression, either behaving as tumor-promoting miRNAs (oncomiRNAs and metastamiRNAs) or as tumor suppressor miRNAs. In general, miRNAs able to promote cancer target mRNAs coding for tumor suppressor proteins, whereas miRNAs exhibiting tumor suppressor properties usually target mRNAs coding oncoproteins. This has a very important implication in diagnosis and/or prognosis, including the recent discovery that the pattern of circulating cell-free miRNAs in serum allows us to perform molecular analyses on these non-invasive liquid biopsies. This research field has confirmed that cancer-specific miRNAs are present in extracellular body fluids, and may play a very important role in the crosstalk between cancer cells and surrounding normal cells. Interestingly, the evidence of the presence of miRNAs in serum, plasma and saliva supports their potential as an additional set of biomarkers for cancer.

This review has focused on the most promising examples potentially leading to the development of anticancer, miRNA-based therapeutic protocols. The inhibition of miRNA activity can be readily achieved by the use of miRNA inhibitors and oligomers, including RNA, DNA, DNA analogues (miRNA antisense therapy), small molecule inhibitors, miRNA sponges or through miRNA masking. On the contrary, the enhancement of miRNA function (miRNA replacement therapy) can be achieved by the use of modified miRNA mimetics and

plasmids or lentiviral vectors carrying miRNA sequences. However, we should carefully consider that a single miRNA can target several mRNAs (not only tumor-associated mRNAs) and a single mRNA may contain in the 3'UTR sequence several signals for miRNA recognition. In this case, antagomiRNA-based therapy should be designed to target multiple miRNAs. MicroRNA targeting and mimicking is further complicated by the facts that, since their discovery and first characterization, the number of miRNA sequences deposited in the miRBase databases is increasing, and research studies on miRNAs in cancer have confirmed the very high complexity of the networks constituted by miRNAs and RNA targets.

One possible approach includes the combination strategies based on the co-administration of anticancer agents, as shown by the observation that i) the combined administration of different antagomiR molecules induces greater antitumor effects and ii) some anti-miR molecules can sensitize drug-resistant tumor cell lines to drug treatment. In this review, we approached two additional issues: i) the combination of miRNA replacement therapy with drug administration and ii) the combination of antagomiR and miRNA replacement therapy. One of the solid results emerging from different independent studies is the demonstration that miRNA replacement therapy can enhance the antitumor effects of the antitumor drugs.

The second important conclusion of the reviewed studies is that the combination of anti-miRNA and miRNA replacement strategies may lead to excellent results, in terms of antitumor effects. This possible combined strategy is in its infancy and very few studies are available in the literature. Proof-of-principle data are presented as examples of possible combined treatments in Fig. 6. Our data indicate that the co-treatment of U251 glioblastoma cells with PNAs targeting miR-221 or miR-222 in the presence of pre-miR-124 transfection leads to a much higher level of apoptosis as opposed to singularly administered reagents. These data further extend the possible combined antitumor treatment based on antitumor drugs and antagomiR-molecules, and present the very novel possibility of combining antagomiR and miRNA replacement therapies.

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