

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

ROBERTO GAMBARI¹, ELEONORA BROGNARA¹, DEMETRIOS A. SPANDIDOS² and ENRICA FABBRI¹

¹Department of Life Sciences and Biotechnology and Biotechnology Center, Ferrara University, Ferrara, Italy;

²Laboratory of Clinical Virology, University of Crete School of Medicine, Heraklion, Crete, Greece

Received March 9, 2016; Accepted April 29, 2016

DOI: 10.3892/ijo.2016.3503

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.

Contents

1. Introduction
2. Tumor suppressor miRNAs
3. OncomiRNAs and metastamiRNAs
4. Mimicking tumor suppressor miRNAs in miRNA replacement therapy
5. Targeting oncomiRNAs
6. MicroRNAs and epithelial-mesenchymal transition
7. MicroRNAs and neoangiogenesis
8. Selected examples of miRNA therapeutics: mimicking miR-124
9. Selected examples of miRNA therapeutics: mimicking miR-93
10. Selected examples of anti-miRNA therapeutics: targeting miR-221/222
11. Combined treatments: targeting multiple miRNAs
12. Combined treatments: co-administration of antitumor drugs and miRNA therapeutic agents
13. Combining miRNA replacement strategies with anti-miRNAs and siRNA molecules
14. Conclusion

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 miRNAs can be targeted at the 3' untranslated region (3'UTR),

Correspondence to: Professor Roberto Gambari, Department of Life Sciences and Biotechnology and Biotechnology Center, Ferrara University, Via Fossato di Mortara 74, I-44121 Ferrara, Italy
E-mail: gam@unife.it

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

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 increased (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).

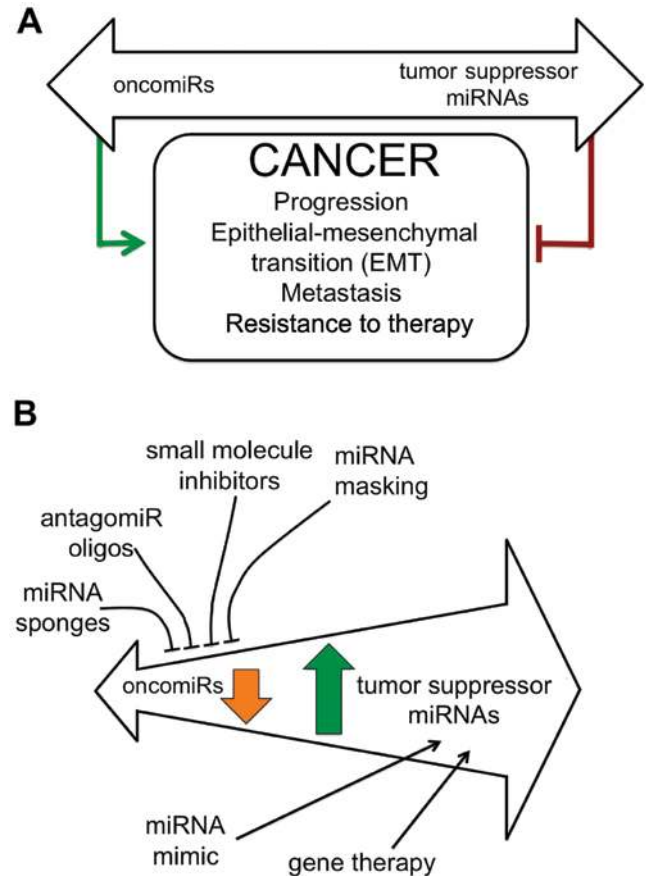


Figure 1. (A) Scheme outlining the ability of miRNAs to promote cancer and metastasis (green arrowed line) or to suppress mRNAs coding oncoproteins (red line). (B) Examples of proposed approaches for the development of therapeutic protocols to modulate the biological activity of miRNAs involved in cancer. 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 <i>et al</i> (112); Hudson <i>et al</i> (113); Chang <i>et al</i> (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 <i>et al</i> (115); Okuda <i>et al</i> (116); Zhou <i>et al</i> (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 <i>et al</i> (86); Trang <i>et al</i> (92); Dangi-Garimella <i>et al</i> (118); Takamizawa <i>et al</i> (119); Shi <i>et al</i> (120); Johnson <i>et al</i> (121)
miR-9	Gastric cancer	Suppression of invasion metastasis	Cyclin D1, Ets1	Zheng <i>et al</i> (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 <i>et al</i> (123); Calin <i>et al</i> (124); Pekarsky <i>et al</i> (125); Bonci <i>et al</i> (126); Kang <i>et al</i> (127)
miR-16	Glioblastoma	Repression of endothelial function and angiogenesis	Bmi-1	Chen <i>et al</i> (128)
miR-18a	Colorectal cancer	Decrease of cell migration, altered cell morphology, G1/S phase cell cycle arrest, increased apoptosis	CDC42	Humphreys <i>et al</i> (129)
miR-25	Prostate cancer	Inhibition of extravasion <i>in vivo</i>	α_v , α_6 integrins	Zoni <i>et al</i> (130)
miR-27a	Acute leukemia	Inhibition of cell growth due at least in part, to increased cellular apoptosis	Bax and Bad	Scheibner <i>et al</i> (94)
miR-29c	Nasopharyngeal carcinoma	Inhibition of invasion and metastasis	Collagens, Laminin $\gamma 1$	Sengupta <i>et al</i> (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 impairment 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 <i>et al</i> (132); Garzon <i>et al</i> (133); Garzon <i>et al</i> (134); Huang <i>et al</i> (98); Kapinas <i>et al</i> (135); Mott <i>et al</i> (136); Fabbri <i>et al</i> (137); Xiong <i>et al</i> (138); Filkowski <i>et al</i> (139); Wang <i>et al</i> (140); Hu <i>et al</i> (141)
miR-30b	Laryngeal carcinoma	Antitumor and pro-apoptotic effect <i>in vivo</i> and <i>in vitro</i>	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 <i>et al</i> (143); Valastyan <i>et al</i> (144); Sossey-Alaoui <i>et al</i> (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 <i>et al</i> (95); Ibrahim <i>et al</i> (91)
miR-33b	Breast cancer lung metastasis, osteosarcoma	Inhibition of stemness, migration, invasion and metastasis	HMGA2, SALL4, Twist1, c-MYC	Lin <i>et al</i> (146); Xu <i>et al</i> (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 <i>et al</i> (148); Bommer <i>et al</i> (149); Fujita <i>et al</i> (150); Leucci <i>et al</i> (151); Saito <i>et al</i> (152); Wei <i>et al</i> (153); Yamakuchi <i>et al</i> (154); Lodygin <i>et al</i> (155); Wiggins <i>et al</i> (90); Yang <i>et al</i> (156); Yang <i>et al</i> (157); Liu <i>et al</i> (158); Krzeszinski <i>et al</i> (159)
miR-34b	Breast, ovarian, endometrial cancer	Tumor suppressor in estrogen-dependent cell growth	Cyclin D1 and JAG1 in ER ⁺ /wild-type p53	Lee <i>et al</i> (102); Wang <i>et al</i> (160)
miR-34c	Breast, ovarian cancer, lung metastasis	Inhibition of cell migration; invasion and lung metastasis	Fra-1	Yang <i>et al</i> (156); Yu <i>et al</i> (161)
miR-101-3p	Salivary gland adenoid cystic carcinoma	Suppression of cell proliferation, invasion and enhanced chemotherapeutic sensitivity	Pim-1	Liu <i>et al</i> (162)
miR-122a	Liver tumor and disease	Reduced disease manifestation and tumor incidence	Klf6	Tsai <i>et al</i> (163)
miR-124	Intrahepatic, bladder, colorectal and lung cancer, osteosarcoma, neuroblastoma, glioma	Modulation of the intercellular adhesion of leading cells; inhibition of EMT <i>in vitro</i> and suppression of intrahepatic and pulmonary metastasis <i>in vivo</i> ; suppression of motility and angiogenesis in bladder cancer cells, of migration and invasion of U-2OS and Saos-2 cells	Integrin β 1, ROCK2, EZH2, UHRF1, ROR2, MYO10, DNMT3B, PTB/PKM1/PKM2 cascade	Taniguchi <i>et al</i> (164); Huang <i>et al</i> (165); Kato <i>et al</i> (166); Zheng <i>et al</i> (167); Wang <i>et al</i> (168); Zhang <i>et al</i> (169); Sun <i>et al</i> (170); Sun <i>et al</i> (171); Chen <i>et al</i> (172); Zhang <i>et al</i> (173)
miR-125a	Cervical cancer	Suppression of tumor growth, invasion, metastasis	ARID3B, STAT3	Cowden Dahl <i>et al</i> (174); Fan <i>et al</i> (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, PTPN13, MERTK, SDF-1 α	Sun <i>et al</i> (176); Xiong <i>et al</i> (177); Wang <i>et al</i> (178); Wen <i>et al</i> (179); Jiang <i>et al</i> (180); Du <i>et al</i> (181); Zhang <i>et al</i> (182); Png <i>et al</i> (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 <i>et al</i> (184); Wuchty <i>et al</i> (185); Zhang <i>et al</i> (186); Huang <i>et al</i> (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 <i>et al</i> (188)
miR-135a	Prostate cancer	Inhibition of cell invasion and migration	ROCK1, ROCK2	Kroiss <i>et al</i> (189)
miR-137	Colorectal cancer	Reduction of invasiveness	FMNL2	Liang <i>et al</i> (190)
miR-143	Non-small cell lung cancer	Suppression of cell proliferation; inhibition of cell migration and invasion; induction of apoptosis	Limk1	Xia <i>et al</i> (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 <i>in vitro</i> and suppression of the metastatic cascade <i>in vivo</i> ; inhibition of the invasion and metastasis of neuroblastoma cells	FSCN1, c-MYC, ERK5, N-cadherin, HIF-2 α	Kano <i>et al</i> (188); Ibrahim <i>et al</i> (91); Gao <i>et al</i> (192); Zhang <i>et al</i> (193)
miR-146a/b	Prostate, breast cancer	Inhibition of cell invasion and migration	IRAK1, TRAF6, ROCK1	Bhaumik <i>et al</i> (194); Lin <i>et al</i> (195)
miR-148a	Liver, lung cancer	Inhibition of hepatoma cell migration <i>in vitro</i> and pulmonary metastatic colonization <i>in vivo</i>	MET/Snail signaling	Zhang <i>et al</i> (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 chemotherapeutic response	ITGA5, ROCK1, PIK3CA/p110 α , NRAS, CSF1	Cimino <i>et al</i> (197)
miR-149	Breast, lung cancer	Inhibition of basal-like breast cancer cell migration and invasion <i>in vitro</i> ; impairment of lung colonization <i>in vivo</i>	Rap1a, Rap1b	Bischoff <i>et al</i> (198)
miR-181b	Chronic lymphocytic leukemia	Inhibition of disease progression	Mcl-1, Bcl-2	Visone <i>et al</i> (199)
miR-182	Glioblastoma	Inhibition of cell growth and cell differentiation	Bcl-2L12, c-MET, HIF2A	Kouri <i>et al</i> (200)
miR-193b	Breast cancer, pancreatic ductal adenocarcinoma	Alteration of ER α signaling, such as steroid synthesis and downregulation of the ER α receptor; negative regulation of long non-coding oncogenic RNA	AKR1C2, AKR1C1, YWHAZ (14-3-3 family protein), RNA MIR31HG	Leivonen <i>et al</i> (201); Yang <i>et al</i> (202)
miR-198	Hepatocellular carcinoma	Inhibition of migration and invasion	HGF/c-MET	Tan <i>et al</i> (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 <i>et al</i> (204); Xia <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (207)
miR-214	Colorectal cancer, liver metastasis	Suppression of cell migration and invasion <i>in vitro</i> ; inhibition of liver metastasis of colorectal cancer cells <i>in vivo</i>	FGFR1	Chen <i>et al</i> (208)
miR-218	Gastric cancer	Suppression of tumor metastases	ROBO1	Tie <i>et al</i> (209)
miR-296-5p	Prostate cancer	Reduction of growth invasion and progression	HMGA1	Wei <i>et al</i> (210)
miR-302	Breast cancer	Sensitization of radioresistant breast cancer cells to ionizing radiation	AKT1, RAD52	Liang <i>et al</i> (99)
miR-302b	Hepatocellular carcinoma	Suppression of cell proliferation	EGFR	Wang <i>et al</i> (211)
miR-335	Breast cancer	Inhibition of cell invasion, migration and metastasis	SOX4, PTPRN2, MERTK, TNC	Tavazoie <i>et al</i> (212); Hurst <i>et al</i> (213)
miR-383	Medulloblastoma	Control of cell growth	PRDX3	Li <i>et al</i> (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 <i>et al</i> (215) Luo <i>et al</i> (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 <i>et al</i> (217); Gu <i>et al</i> (218); Sakai <i>et al</i> (219)
miR-504	Hypopharyngeal squamous cell carcinoma	Inhibition of cancer cells proliferation	CDK6	Kikkawa <i>et al</i> (220)
miR-520c/373	Breast cancer	Inhibition of cell invasion <i>in vitro</i> and the cell intravasation <i>in vivo</i>	RELA, TGFBR2	Keklikoglou <i>et al</i> (221)
miR-545	Pancreatic ductal adenocarcinoma, lung cancer cells	Inhibition of cell growth and proliferation	RIG-1, CDK4	Song <i>et al</i> (222); Bowen <i>et al</i> (223)
miR-596	Oral squamous cell carcinoma (OSCC)	Growth inhibition	LGALS3BP	Endo <i>et al</i> (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 <i>et al</i> (240); Wang <i>et al</i> (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-suppressive pathways, resisting cell death	PTEN, TPM1, PDCD4, p63, RECK, p53, TGF- β	Chan <i>et al</i> (242); Zhu <i>et al</i> (230); Frankel <i>et al</i> (231); Volinia <i>et al</i> (233)
miR-23b	Renal cancer cells	Downregulation of POX (tumor suppressor), increase in HIF signaling	POX	Liu <i>et al</i> (243)
miR-27a	Prostate cancer	Increase in the expression of AR target genes and prostate cancer cell growth	PHB	Fletcher <i>et al</i> (244)
miR-100	Myeloid leukemia, glioma	Promotion of cell differentiation, survival and apoptosis	RBSP3, ATM	Ng <i>et al</i> (245); Zheng <i>et al</i> (246)
miR-125b	B-cell leukemia	Induction of cell differentiation and transformation	MAP3K11, ARID3B	Knackmuss <i>et al</i> (247)
miR-132	Pancreatic adenocarcinoma (PDAC)	Stimulation of cell proliferation via the β 2 adrenergic pathway	Rb1	Park <i>et al</i> 2011 (248)
miR-212	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 <i>et al</i> (249); Jiang <i>et al</i> (250); Czyzyk-Krzeska <i>et al</i> (251); Wang <i>et al</i> (252); Ling <i>et al</i> (253); Musilova <i>et al</i> (254)
miR-155				
miR-17	Neuroblastoma	Marked increase of <i>in vitro</i> and <i>in vivo</i> tumorigenesis	p21, BIM	Fontana <i>et al</i> (255)
miR-182	Melanoma	Promotion of melanoma metastases	MITF, FOXO3	Segura <i>et al</i> (256)
miR-214	Ovarian cancer	Stimulation of cell survival and cisplatin resistance	PTEN	Yang <i>et al</i> (257)
miR-221	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, PTP μ , FOXO3, PIK3R1, TIMP3, TIMP2, DDIT4, MDM2, ER α , SOCS3, OCS1, HDAC6, ANGPTL2, BBC3, BMF, RECK, PDLIM2, RelA, p57 ^{Kip2}	Zhang <i>et al</i> (258); Garofalo <i>et al</i> (259); Quintavalle <i>et al</i> (260); Chen <i>et al</i> (261); Matsuzaki <i>et al</i> (262)
miR-222				
miR-296	Brain tumors	Promotion of angiogenesis	HGS	Wurdinger <i>et al</i> (263)
miR-301	Breast cancer	Promotion of growth, proliferation, invasion and metastases	FOXF2, BBC3, PTEN	Shi <i>et al</i> (264)
miR-372	Testicular tumors	Promotion of tumorigenesis in cooperation with RAS	LATS2	Voorhoeve <i>et al</i> (265)
miR-373				
miR-375	Gastric cancer	Promotion of carcinogenesis	JAK2, PDK1	Xu <i>et al</i> (266)

Table II. Continued.

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

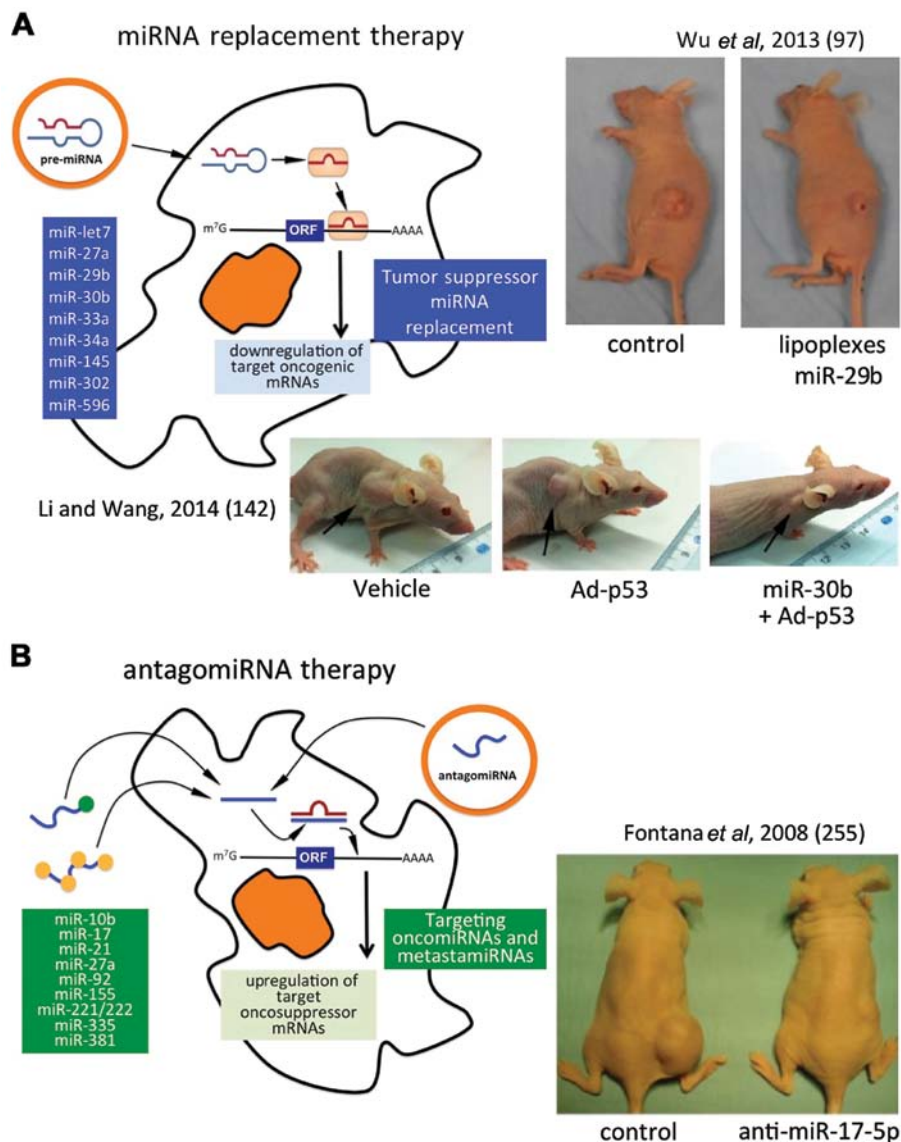


Figure 2. (A) miRNA replacement therapy: partial list of tumor suppressor miRNAs (in the blue box) and selected examples of the *in vivo* restoration of miR-29b (97) and of miR-30b (142), leading to the inhibition of tumor cell growth. (B) Targeting oncomiRNAs and metastamiRNAs with antagomiRNAs: partial 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 <i>et al</i> (272); Chen <i>et al</i> (273); White <i>et al</i> (274)
miR-10b	Breast cancer, glioblastoma	Promotion of EMT, migration, invasion and metastasis	TP53, PAX6, NOTCH1, HOXD10	Ma <i>et al</i> (275); Lin <i>et al</i> (276)
miR-15b	Pancreatic cancer	Promotion of EMT	SMURF2	Zhang <i>et al</i> (277)
miR-19a/b	Gastric cancer	Facilitation of cell migration, invasion and metastasis	MXD1	Wu <i>et al</i> (278)
miR-20a	Cervical, gallbladder cancer	Facilitation of cancer cell proliferation and metastasis <i>in vitro</i> and increased tumor growth <i>in vivo</i> ; induction of EMT	ATG7, TIMP2, Smad7	Chang <i>et al</i> (279); Zhao <i>et al</i> (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 intravasation	TPM1, PDCD4, Maspin (SERPINB5), PTEN, PI3K, Sprouty, p53, cyclin D1, FOXO1, FBXO11, TIPE2, MSH2, hTERT, HIF1 α , TIMP3, APAF1	Zhu <i>et al</i> (230); Dean <i>et al</i> (281); Peacock <i>et al</i> (282); Xu <i>et al</i> (283); Asangani <i>et al</i> (284); Hurst <i>et al</i> (213); Melnik <i>et al</i> (285)
miR-96	Prostate cancer	Bone metastasis, enhanced effects on cellular growth and invasiveness	TGF- β /mTOR signaling	Siu <i>et al</i> (237)
miR-105	Breast cancer	Destruction of the integrity of vascular endothelial barriers to promote metastasis	ZO-1	Zhou <i>et al</i> (286)
miR-122	Breast cancer	Promotion of metastatic colonization	PKM2,	Fong <i>et al</i> (287)
miR-135b	Lung cancer	Promotion of cell migration, invasion and metastasis	LATS2, TrCP, NDR2, LZTST1	Lin <i>et al</i> (288)
miR-181a	Breast cancer	Promotion of breast cancer metastasis	Bim/TGF- β	Taylor <i>et al</i> (289)
miR-182	Gallbladder, sarcoma, lung cancer	Promotion of metastasis, circulating tumor cells (CTC); regulation of intravasation	CADM1, RSU1, MTSS1, PAI1, TIMP1	Qiu <i>et al</i> (290); Sachdeva <i>et al</i> (239)
miR-183	Oesophageal carcinoma	Promotion of proliferation and invasion	PDCD4	Ren <i>et al</i> (291)
miR-200s	Breast, ovarian cancer	Activation of invasion and metastasis (but in other cases inhibition)	ZEB1, ZEB2, SIP1, Sec23a	Korpál <i>et al</i> (292); Korpál <i>et al</i> (293); Park <i>et al</i> (294); Gregory <i>et al</i> (295)
miR-214	Lung adenocarcinoma, melanoma	Promotion of migration, invasion and resistance to anoikis of melanoma cells <i>in vitro</i> and the extravasation and lung metastasis formation <i>in vivo</i> ; promotion of EMT and metastasis	TFAP2C, Sufu	Penna <i>et al</i> (296); Penna <i>et al</i> (297); Long <i>et al</i> (298)
miR-296-3p	Prostate cancer	Promotion of metastasis	ICAM1	Liu <i>et al</i> (299)
miR-296-5p	Prostate cancer	Promotion of growth and invasion, metastatic progression, and persistence of cancer-initiating cells	Numbl (Klf4 signaling)	Vaira <i>et al</i> (300)

Table III. Continued.

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

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

Tumor type	miRNA target	Modulated mRNA	Effects following miR treatment	Authors/(Refs.)
Lung cancer	miR-34a	Repression of c-Met, Bcl-2; partial repression of CDK4	Block of tumor growth	Wiggins <i>et al</i> (90)
Colon carcinoma	miR-33a	Pim-1	Reduced tumor proliferation	Ibrahim <i>et al</i> (91)
Colon carcinoma	miR-145	c-Myc and ERK5	Reduced tumor proliferation and increased apoptosis	Ibrahim <i>et al</i> (91)
Lung cancer	miR-let7	Negative regulation of the cell cycle oncogenes <i>RAS</i> , <i>MYC</i> and <i>HMG2A</i>	Reduction of tumor growth	Trang <i>et al</i> (92)
Acute leukemia	miR-27a	Bax and Bad	Inhibition of cell growth due, at least in part, to increased cellular apoptosis	Scheibner <i>et al</i> (94)
CML cells	miR-33a	Pim-1	Decelerated cell proliferation	Thomas <i>et al</i> (95)
Oral squamous cell carcinoma (OSCC)	miR-596	LGALS3BP	Growth inhibition	Endo <i>et al</i> (96)
Non-small cell lung adenocarcinomas, A549 cells	miR-29b	CDK6, DNMT3B, MCL-1	Inhibition of tumorigenicity <i>in vivo</i>	Wu <i>et al</i> (97)
Acute myeloid leukemia	miR-29b	Downregulation of DNMTs, CDK6, SP1, KIT and FLT3	Decreased AML cell growth and impairment of colony formation; longer survival of treated mice; improvement of antileukemic activity of decitabine	Huang <i>et al</i> (98)
Laryngeal carcinoma	miR-30b	p53 via MDM2	Antitumor and pro-apoptotic effect <i>in vivo</i> and <i>in vitro</i>	Li and Wang (142)
Breast cancer	miR-302	AKT1 and RAD52	Sensitized radioresistant breast cancer cells to ionizing radiation	Liang <i>et al</i> (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 <i>in vitro</i> and <i>in vivo</i> tumorigenesis	Fontana <i>et al</i> (255)
Human glioblastoma	miR-27a	FOXO3a	Suppression of U87 growth <i>in vitro</i> and <i>in vivo</i>	Ge <i>et al</i> (309)
Malignant astrocytoma cells	miR-335	Daam1	Growth arrest, cell apoptosis, invasion repression and marked regression of astrocytoma xenografts	Shu <i>et al</i> (310)
Cutaneous squamous cell carcinoma (SCC)	miR-155	CDC73	Decreased cell viability, increased apoptosis, and marked regression of xenografts in nude mice	Rather <i>et al</i> (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 <i>et al</i> (312)
Glioma	miR-381	LRRC4	Decreased cell proliferation and tumor growth	Tang <i>et al</i> (313)
Breast cancer	miR-10b	Hoxd10	Suppression of formation of lung metastases	Ma <i>et al</i> (314)
Prostate cancer	miR-221/miR-222	p27	Reduction of tumor growth	Mercatelli <i>et al</i> (315)
Pancreatic cancer	miR-221/miR-21	SOCS6, SMAD7, CDK6, KLF12, MAPK10	Modulation of tumorigenesis, metastasis, and chemotherapy resistance in stem-like cells	Zhao <i>et al</i> (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

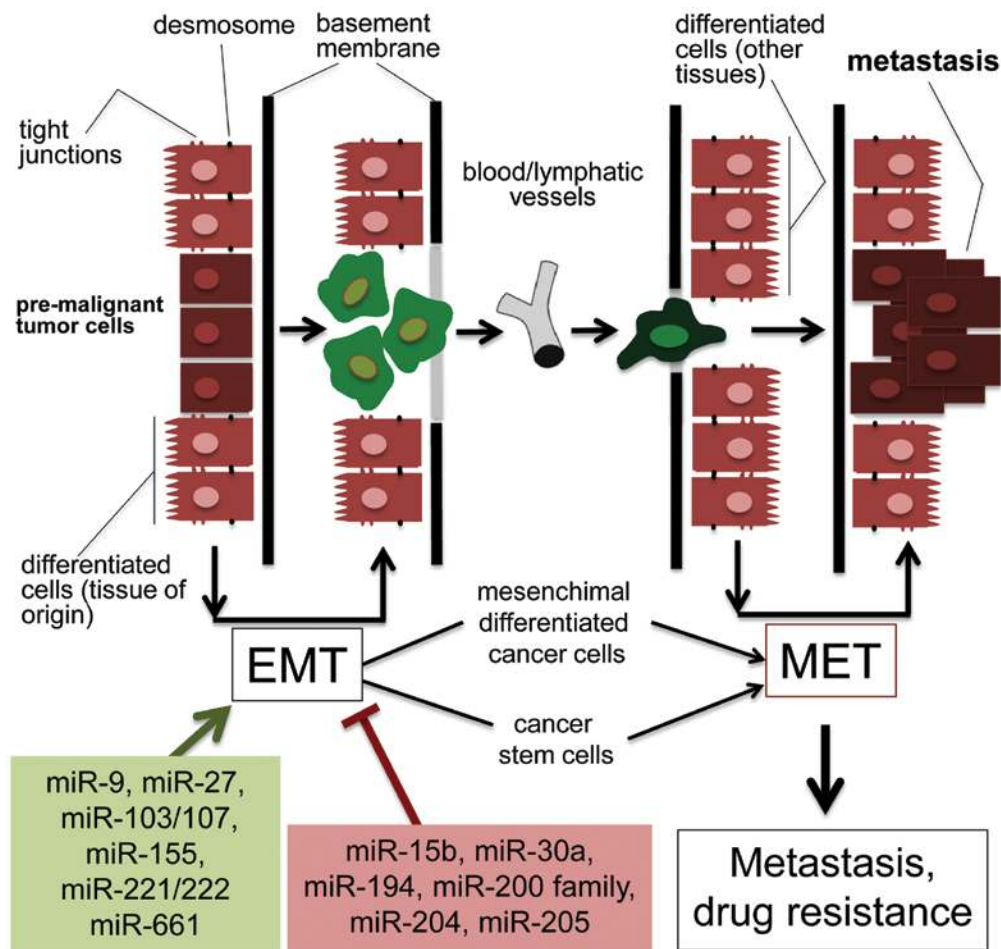


Figure 3. Epithelial-mesenchymal transition (EMT), a powerful process leading to tumor invasion and metastasis. Examples of EMT-promoting miRNAs are reported in the green box, while examples of EMT-interfering miRNAs are reported in the pink box. Modified from Kiesslich *et al* (323).

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-1 α 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- κ B (NF- κ B) network should be proposed, since i) NF- κ B is one of the major transcription factors involved in IL-8 gene regulation (329); ii) NF- κ B is a marker of glioma onset and progression (330-333); iii) miR-16 inhibits glioma cell growth through the suppression of the NF- κ B 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 metalloproteinase 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 carried 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)

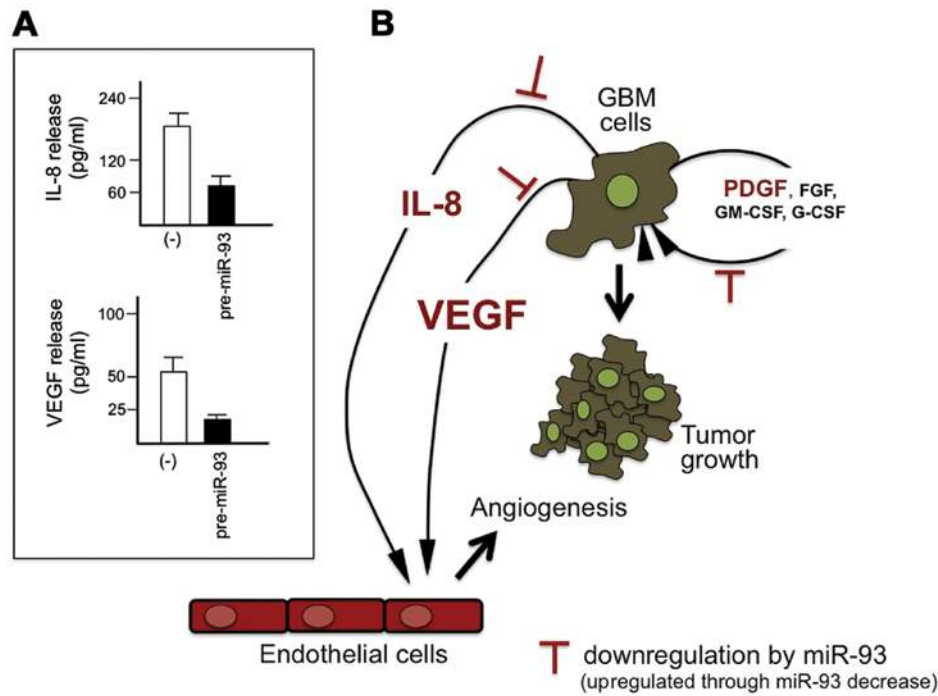


Figure 4. (A) Transfection of U251 glioma cells with pre-miR-93 leads to the downregulation of interleukin-8 (IL-8) (upper panel) and vascular endothelial growth factor (VEGF; lower panel) protein expression. (B) Scheme outlining the effects of pre-miR-93 on neoangiogenesis and tumor growth in gliomas. 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^{Kip1} 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

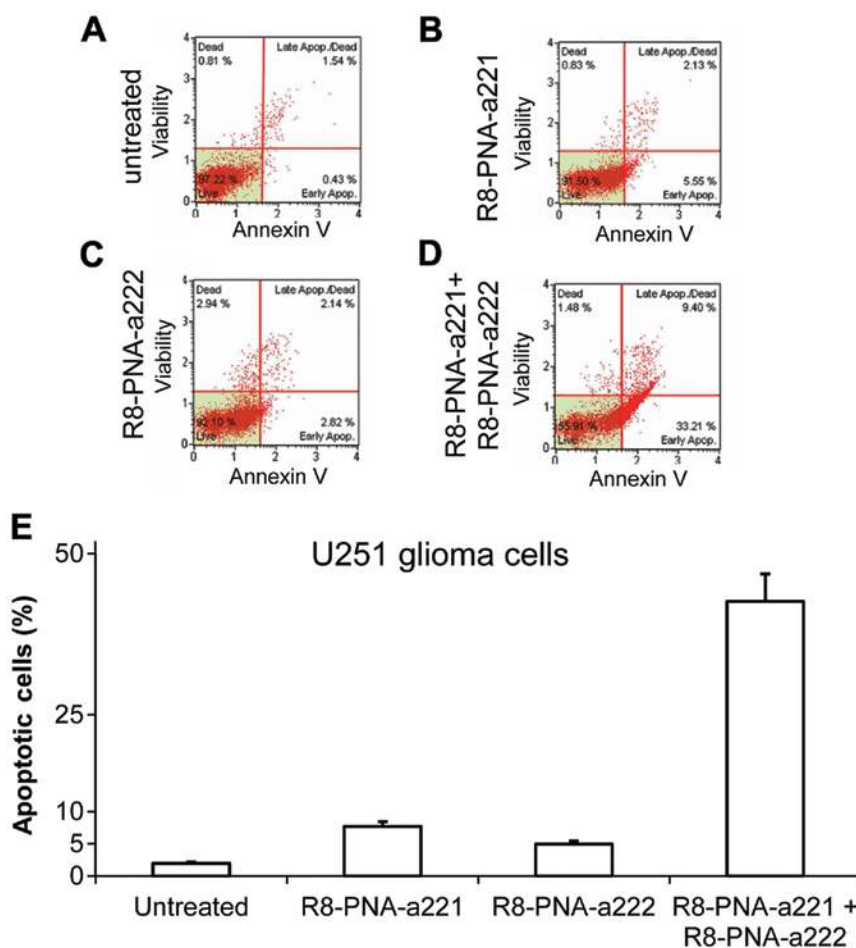


Figure 5. (A-D) Co-administration of R8-conjugated PNAs against miR-221 (R8-PNA-a221) and miR-222 (R8-PNA-a222) exhibits increased effects on the apoptosis of treated U251 glioma cells. Human glioma U251 cells were cultured (A) without, or (B) in the presence of $4 \mu\text{M}$ R8-PNA-a221, (C) $4 \mu\text{M}$ R8-PNA-a222 or (D) $2 \mu\text{M}$ R8-PNA-a221 plus $2 \mu\text{M}$ 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 inhibition 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 (MDR1), 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-administration 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 anti-proliferative 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 accu-

mulation 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

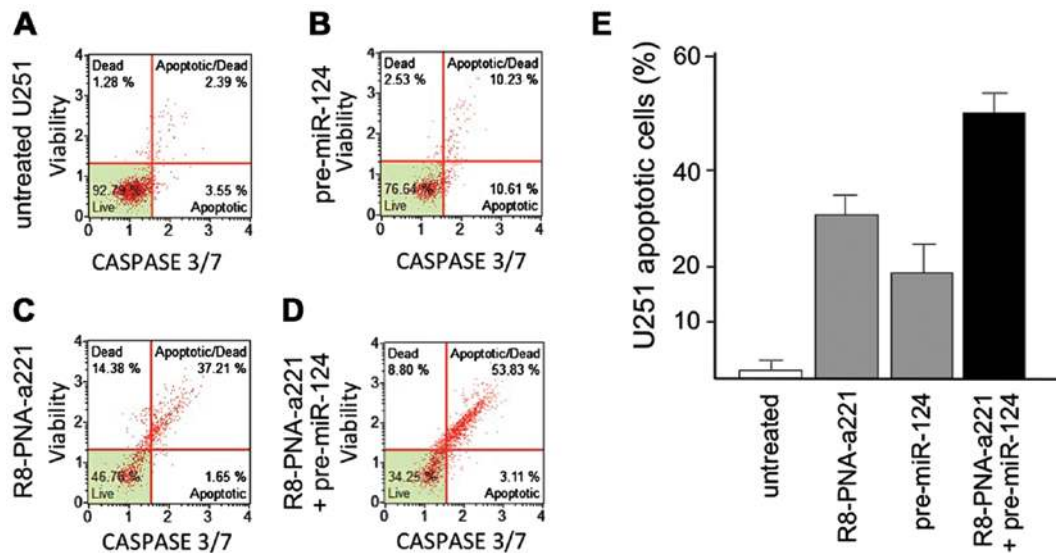


Figure 6. Treatment of U251 glioma cells with (B) 10 nM pre-miR-124, (C) 4 μ M R8-PNA-a221 targeting miR-221 or (D) a combined administration of 10 nM pre-miR-124 and 4 μ M R8-PNA-a221. (A) Control untreated cells are shown. After 48 h of treatment, the effects on apoptosis were analyzed by the caspase-3/7 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.

Acknowledgements

This study was funded by CIB, by COFIN-2009 and by AIRC (IG 13575: peptide nucleic acids targeting oncomiR and tumor-suppressor miRNAs: cancer diagnosis and therapy). EB is supported by an Umberto Veronesi fellowship. We would like to thank the Horizon-2020 ULTRAPLACAD (ULTRASensitive PLASmonic devices for early Cancer Diagnosis) n.633937 project for supporting the research on circulating miRNAs as diagnostic tools.

References

- Mazière P and Enright AJ: Prediction of microRNA targets. *Drug Discov Today* 12: 452-458, 2007.
- Witkos TM, Koscianska E and Krzyzosiak WJ: Practical aspects of microRNA target prediction. *Curr Mol Med* 11: 93-109, 2011.
- Ghelani HS, Rachchh MA and Gokani RH: MicroRNAs as newer therapeutic targets: A big hope from a tiny player. *J Pharmacol Pharmacother* 3: 217-227, 2012.
- Krol J, Loedige I and Filipowicz W: The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet* 11: 597-610, 2010.
- Sun K and Lai EC: Adult-specific functions of animal microRNAs. *Nat Rev Genet* 14: 535-548, 2013.
- Chekulaeva M and Filipowicz W: Mechanisms of miRNA-mediated post-transcriptional regulation in animal cells. *Curr Opin Cell Biol* 21: 452-460, 2009.
- Guo H, Ingolia NT, Weissman JS and Bartel DP: Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature* 466: 835-840, 2010.
- Cammaerts S, Strazisar M, De Rijk P and Del Favero J: Genetic variants in microRNA genes: Impact on microRNA expression, function, and disease. *Front Genet* 6: 186, 2015.
- Friedländer MR, Lizano E, Houben AJS, Bezdan D, Báñez-Coronel M, Kudla G, Mateu-Huertas E, Kagerbauer B, González J, Chen KC, *et al*: Evidence for the biogenesis of more than 1,000 novel human microRNAs. *Genome Biol* 15: R57, 2014.
- Cheng WC, Chung IF, Tsai CF, Huang TS, Chen CY, Wang SC, Chang TY, Sun HJ, Chao JY, Cheng CC, *et al*: YM500v2: a small RNA sequencing (smRNA-seq) database for human cancer miRNome research. *Nucleic Acids Res* 43: D862-D867, 2015.
- Londin E, Loher P, Telonis AG, Quann K, Clark P, Jing Y, Hatzimichael E, Kirino Y, Honda S, Lally M, *et al*: Analysis of 13 cell types reveals evidence for the expression of numerous novel primate- and tissue-specific microRNAs. *Proc Natl Acad Sci USA* 112: E1106-E1115, 2015.
- Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A and Enright AJ: miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Res* 34: D140-D144, 2006.
- Kozomara A and Griffiths-Jones S: miRBase: Annotating high confidence microRNAs using deep sequencing data. *Nucleic Acids Res* 42: D68-D73, 2014.
- Taccioli C, Fabbri E, Visone R, Volinia S, Calin GA, Fong LY, Gambari R, Bottoni A, Acunzo M, Hagan J, *et al*: UCbase and miRfunc: A database of ultraconserved sequences and microRNA function. *Nucleic Acids Res* 37: D41-D48, 2009.
- Witwer KW: Data submission and quality in microarray-based microRNA profiling. *Clin Chem* 59: 392-400, 2013.
- Xie B, Ding Q, Han H and Wu D: miRCancer: A microRNA-cancer association database constructed by text mining on literature. *Bioinformatics* 29: 638-644, 2013.
- Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS and Johnson JM: Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* 433: 769-773, 2005.
- Peter ME: Targeting of mRNAs by multiple miRNAs: The next step. *Oncogene* 29: 2161-2164, 2010.
- Bianchi N, Finotti A, Ferracin M, Lampronti I, Zuccato C, Breviglieri G, Brognara E, Fabbri E, Borgatti M, Negrini M, *et al*: Increase of microRNA-210, decrease of raptor gene expression and alteration of mammalian target of rapamycin regulated proteins following mithramycin treatment of human erythroid cells. *PLoS One* 10: e0121567, 2015.
- Subramanian S and Steer CJ: MicroRNAs as gatekeepers of apoptosis. *J Cell Physiol* 223: 289-298, 2010.
- Wang Y and Belloch R: Cell cycle regulation by MicroRNAs in embryonic stem cells. *Cancer Res* 69: 4093-4096, 2009.
- Fabbri E, Borgatti M, Montagner G, Bianchi N, Finotti A, Lampronti I, Bezzetti V, Dececchi MC, Cabrini G and Gambari R: Expression of microRNA-93 and Interleukin-8 during *Pseudomonas aeruginosa*-mediated induction of proinflammatory responses. *Am J Respir Cell Mol Biol* 50: 1144-1155, 2014.
- Faruq O and Vecchione A: microRNA: Diagnostic perspective. *Front Med Lausanne* 2: 51, 2015.
- Shalaby T, Fiaschetti G, Baumgartner M and Grotzer MA: Significance and therapeutic value of miRNAs in embryonal neural tumors. *Molecules* 19: 5821-5862, 2014.
- Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M, *et al*: Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci USA* 101: 2999-3004, 2004.
- Palmero EI, de Campos SG, Campos M, de Souza NC, Guerreiro ID, Carvalho AL and Marques MM: Mechanisms and role of microRNA deregulation in cancer onset and progression. *Genet Mol Biol* 34: 363-370, 2011.
- Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, Galas DJ and Wang K: The microRNA spectrum in 12 body fluids. *Clin Chem* 56: 1733-1741, 2010.
- Fayyad-Kazan H, Bitar N, Najjar M, Lewalle P, Fayyad-Kazan M, Badran R, Hamade E, Daher A, Hussein N, ElDirani R, *et al*: Circulating miR-150 and miR-342 in plasma are novel potential biomarkers for acute myeloid leukemia. *J Transl Med* 11: 31, 2013.

29. Neviani P and Fabbri M: Exosomal microRNAs in the tumor microenvironment. *Front Med Lausanne* 2: 47, 2015.
30. Köberle V, Kronenberger B, Pleli T, Trojan J, Imelmann E, Peveling-Oberhag J, Welker MW, Elhendawy M, Zeuzem S, Piiper A, *et al.*: Serum microRNA-1 and microRNA-122 are prognostic markers in patients with hepatocellular carcinoma. *Eur J Cancer* 49: 3442-3449, 2013.
31. He Y, Lin J, Kong D, Huang M, Xu C, Kim TK, Etheridge A, Luo Y, Ding Y and Wang K: Current state of circulating MicroRNAs as cancer biomarkers. *Clin Chem* 61: 1138-1155, 2015.
32. Westphal M and Lamszus K: Circulating biomarkers for gliomas. *Nat Rev Neurol* 11: 556-566, 2015.
33. Yau TO, Wu CW, Dong Y, Tang CM, Ng SS, Chan FK, Sung JJ and Yu J: microRNA-221 and microRNA-18a identification in stool as potential biomarkers for the non-invasive diagnosis of colorectal carcinoma. *Br J Cancer* 111: 1765-1771, 2014.
34. Cheng H, Zhang L, Cogdell DE, Zheng H, Schetter AJ, Nykter M, Harris CC, Chen K, Hamilton SR and Zhang W: Circulating plasma MiR-141 is a novel biomarker for metastatic colon cancer and predicts poor prognosis. *PLoS One* 6: e17745, 2011.
35. Czech MP: MicroRNAs as therapeutic targets. *N Engl J Med* 354: 1194-1195, 2006.
36. Brown BD and Naldini L: Exploiting and antagonizing microRNA regulation for therapeutic and experimental applications. *Nat Rev Genet* 10: 578-585, 2009.
37. Kota SK and Balasubramanian S: Cancer therapy via modulation of micro RNA levels: A promising future. *Drug Discov Today* 15: 733-740, 2010.
38. Small EM and Olson EN: Pervasive roles of microRNAs in cardiovascular biology. *Nature* 469: 336-342, 2011.
39. Bader AG and Lammers P: The Therapeutic Potential of microRNAs. *Discovery Technology*, 2011.
40. Rothschild SI: microRNA therapies in cancer. *Mol Cell Ther* 2: 7, 2014.
41. van Rooij E and Kauppinen S: Development of microRNA therapeutics is coming of age. *EMBO Mol Med* 6: 851-864, 2014.
42. Orellana EA and Kasinski AL: MicroRNAs in cancer: A historical perspective on the path from discovery to therapy. *Cancers (Basel)* 7: 1388-1405, 2015.
43. Berindan-Neagoe I, Monroig PC, Pasculli B and Calin GA: MicroRNAome genome: A treasure for cancer diagnosis and therapy. *CA Cancer J Clin* 64: 311-336, 2014.
44. Bernardo BC, Ooi JY, Lin RC and McMullen JR: miRNA therapeutics: A new class of drugs with potential therapeutic applications in the heart. *Future Med Chem* 7: 1771-1792, 2015.
45. Weiler J, Hunziker J and Hall J: Anti-miRNA oligonucleotides (AMOs): Ammunition to target miRNAs implicated in human disease? *Gene Ther* 13: 496-502, 2006.
46. Lu Y, Xiao J, Lin H, Bai Y, Luo X, Wang Z and Yang B: A single anti-microRNA antisense oligodeoxyribonucleotide (AMO) targeting multiple microRNAs offers an improved approach for microRNA interference. *Nucleic Acids Res* 37: e24, 2009.
47. Lennox KA and Behlke MA: Chemical modification and design of anti-miRNA oligonucleotides. *Gene Ther* 18: 1111-1120, 2011.
48. Obad S, dos Santos CO, Petri A, Heidenblad M, Broom O, Ruse C, Fu C, Lindow M, Stenvang J, Straarup EM, *et al.*: Silencing of microRNA families by seed-targeting tiny LNAs. *Nat Genet* 43: 371-378, 2011.
49. Elmén J, Lindow M, Schütz S, Lawrence M, Petri A, Obad S, Lindholm M, Hedtjörn M, Hansen HF, Berger U, *et al.*: LNA-mediated microRNA silencing in non-human primates. *Nature* 452: 896-899, 2008.
50. Stenvang J, Silahatoglu AN, Lindow M, Elmén J and Kauppinen S: The utility of LNA in microRNA-based cancer diagnostics and therapeutics. *Semin Cancer Biol* 18: 89-102, 2008.
51. Chabot S, Teissié J and Golzio M: Targeted electro-delivery of oligonucleotides for RNA interference: siRNA and anti-miR. *Adv Drug Deliv Rev* 81: 161-168, 2015.
52. Lundin KE, Højland T, Hansen BR, Persson R, Bramsen JB, Kjems J, Koch T, Wengel J and Smith CI: Biological activity and biotechnological aspects of locked nucleic acids. *Adv Genet* 82: 47-107, 2013.
53. Staedel C, Varon C, Nguyen PH, Vialet B, Chambonnier L, Rousseau B, Soubeyran I, Evrard S, Couillaud F and Darfeuille F: Inhibition of gastric tumor cell growth using seed-targeting LNA as specific, long-lasting MicroRNA inhibitors. *Mol Ther Nucleic Acids* 4: e246, 2015.
54. Avitabile C, Accardo A, Ringhieri P, Morelli G, Saviano M, Montagner G, Fabbri E, Gallerani E, Gambari R and Romanelli A: Incorporation of naked peptide nucleic acids into liposomes leads to fast and efficient delivery. *Bioconjug Chem* 26: 1533-1541, 2015.
55. Fabbri E, Manicardi A, Tedeschi T, Sforza S, Bianchi N, Brognara E, Finotti A, Breveglieri G, Borgatti M, Corradini R, *et al.*: Modulation of the biological activity of microRNA-210 with peptide nucleic acids (PNAs). *ChemMedChem* 6: 2192-2202, 2011.
56. Brognara E, Fabbri E, Bazzoli E, Montagner G, Ghimenton C, Eccher A, Cantù C, Manicardi A, Bianchi N, Finotti A, *et al.*: Uptake by human glioma cell lines and biological effects of a peptide-nucleic acids targeting miR-221. *J Neurooncol* 118: 19-28, 2014.
57. Cheng CJ, Bahal R, Babar IA, Pincus Z, Barrera F, Liu C, Svoronos A, Braddock DT, Glazer PM, Engelman DM, *et al.*: MicroRNA silencing for cancer therapy targeted to the tumour microenvironment. *Nature* 518: 107-110, 2015.
58. Morris JK, Chomyk A, Song P, Parker N, Deckard S, Trapp BD, Pimplikar SW and Dutta R: Decrease in levels of the evolutionarily conserved microRNA miR-124 affects oligodendrocyte numbers in Zebrafish, *Danio rerio*. *Invert Neurosci* 15: 4, 2015.
59. Conte I, Hadfield KD, Barbato S, Carrella S, Pizzo M, Bhat RS, Carissimo A, Karali M, Porter LF, Urquhart J, *et al.*: MiR-204 is responsible for inherited retinal dystrophy associated with ocular coloboma. *Proc Natl Acad Sci USA* 112: E3236-E3245, 2015.
60. Ristori E, Lopez-Ramirez MA, Narayanan A, Hill-Teran G, Moro A, Calvo CF, Thomas JL and Nicoli S: A Dicer-miR-107 interaction regulates biogenesis of specific miRNAs crucial for neurogenesis. *Dev Cell* 32: 546-560, 2015.
61. Ebert MS, Neilson JR and Sharp PA: MicroRNA sponges: Competitive inhibitors of small RNAs in mammalian cells. *Nat Methods* 4: 721-726, 2007.
62. Ebert MS and Sharp PA: MicroRNA sponges: Progress and possibilities. *RNA* 16: 2043-2050, 2010.
63. Kluiver J, Gibcus JH, Hettinga C, Adema A, Richter MK, Halsema N, Slezak-Prochazka I, Ding Y, Kroesen BJ and van den Berg A: Rapid generation of microRNA sponges for microRNA inhibition. *PLoS One* 7: e29275, 2012a.
64. Kluiver J, Slezak-Prochazka I, Smigielska-Czepiel K, Halsema N, Kroesen BJ and van den Berg A: Generation of miRNA sponge constructs. *Methods* 58: 113-117, 2012.
65. Li KC, Chang YH, Yeh CL and Hu YC: Healing of osteoporotic bone defects by baculovirus-engineered bone marrow-derived MSCs expressing MicroRNA sponges. *Biomaterials* 74: 155-166, 2016.
66. de Melo Maia B, Ling H, Monroig P, Ciccone M, Soares FA, Calin GA and Rocha RM: Design of a miRNA sponge for the miR-17 miRNA family as a therapeutic strategy against vulvar carcinoma. *Mol Cell Probes* 29: 420-426, 2015.
67. Tay FC, Lim JK, Zhu H, Hin LC and Wang S: Using artificial microRNA sponges to achieve microRNA loss-of-function in cancer cells. *Adv Drug Deliv Rev* 81: 117-127, 2015.
68. Liu Y, Han Y, Zhang H, Nie L, Jiang Z, Fa P, Gui Y and Cai Z: Synthetic miRNA-mowers targeting miR-183-96-182 cluster or miR-210 inhibit growth and migration and induce apoptosis in bladder cancer cells. *PLoS One* 7: e52280, 2012.
69. Choi WY, Giraldez AJ and Schier AF: Target protectors reveal dampening and balancing of Nodal agonist and antagonist by miR-430. *Science* 318: 271-274, 2007.
70. Haraguchi T, Ozaki Y and Iba H: Vectors expressing efficient RNA decoys achieve the long-term suppression of specific microRNA activity in mammalian cells. *Nucleic Acids Res* 37: e43, 2009.
71. Krol J, Busskamp V, Markiewicz I, Stadler MB, Ribí S, Richter J, Dübél J, Bicker S, Fehling HJ, Schübeler D, *et al.*: Characterizing light-regulated retinal microRNAs reveals rapid turnover as a common property of neuronal microRNAs. *Cell* 141: 618-631, 2010.
72. Cassidy JJ, Straughan AJ and Carthew RW: Differential masking of natural genetic variation by miR-9a in *Drosophila*. *Genetics* 202: 675-687, 2016.
73. Wang Z: The principles of MiRNA-masking antisense oligonucleotides technology. *Methods Mol Biol* 676: 43-49, 2011.
74. Bak RO, Hollensen AK and Mikkelsen JG: Managing microRNAs with vector-encoded decoy-type inhibitors. *Mol Ther* 21: 1478-1485, 2013.

75. Murakami K and Miyagishi M: Tiny masking locked nucleic acids effectively bind to mRNA and inhibit binding of microRNAs in relation to thermodynamic stability. *Biomed Rep* 2: 509-512, 2014.
76. Shin KJ, Wall EA, Zavzavadjian JR, Santat LA, Liu J, Hwang JI, Rebres R, Roach T, Seaman W, Simon MI, *et al*: A single lentiviral vector platform for microRNA-based conditional RNA interference and coordinated transgene expression. *Proc Natl Acad Sci USA* 103: 13759-13764, 2006.
77. Askou AL, Aagaard L, Kostic C, Arsenijevic Y, Hollensen AK, Bek T, Jensen TG, Mikkelsen JG and Corydon TJ: Multigenic lentiviral vectors for combined and tissue-specific expression of miRNA- and protein-based antiangiogenic factors. *Mol Ther Methods Clin Dev* 2: 14064, 2015.
78. Winbanks CE, Beyer C, Hagg A, Qian H, Sepulveda PV and Gregorevic P: miR-206 represses hypertrophy of myogenic cells but not muscle fibers via inhibition of HDAC4. *PLoS One* 8: e73589, 2013.
79. Montgomery RL, Yu G, Latimer PA, Stack C, Robinson K, Dalby CM, Kaminski N and van Rooij E: MicroRNA mimicry blocks pulmonary fibrosis. *EMBO Mol Med* 6: 1347-1356, 2014.
80. Bader AG: miR-34 - a microRNA replacement therapy is headed to the clinic. *Front Genet* 3: 120, 2012.
81. Kwekkeboom RF, Lei Z, Doevendans PA, Musters RJ and Sluijter JP: Targeted delivery of miRNA therapeutics for cardiovascular diseases: Opportunities and challenges. *Clin Sci (Lond)* 127: 351-365, 2014.
82. Sherr CJ: Principles of tumor suppression. *Cell* 116: 235-246, 2004.
83. Lee YS and Dutta A: The tumor suppressor microRNA let-7 represses the HMGA2 oncogene. *Genes Dev* 21: 1025-1030, 2007.
84. Mayr C, Hemann MT and Bartel DP: Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. *Science* 315: 1576-1579, 2007.
85. Park SM, Shell S, Radjabi AR, Schickel R, Feig C, Boyerinas B, Dinulescu DM, Lengyel E and Peter ME: Let-7 prevents early cancer progression by suppressing expression of the embryonic gene HMGA2. *Cell Cycle* 6: 2585-2590, 2007.
86. Sampson VB, Rong NH, Han J, Yang Q, Aris V, Soteropoulos P, Petrelli NJ, Dunn SP and Krueger LJ: MicroRNA let-7a down-regulates MYC and reverts MYC-induced growth in Burkitt lymphoma cells. *Cancer Res* 67: 9762-9770, 2007.
87. Müller DW and Bosserhoff AK: Integrin beta 3 expression is regulated by let-7a miRNA in malignant melanoma. *Oncogene* 27: 6698-6706, 2008.
88. Peng Y, Laser J, Shi G, Mittal K, Melamed J, Lee P and Wei JJ: Antiproliferative effects by Let-7 repression of high-mobility group A2 in uterine leiomyoma. *Mol Cancer Res* 6: 663-673, 2008.
89. Bader AG, Brown D and Winkler M: The promise of microRNA replacement therapy. *Cancer Res* 70: 7027-7030, 2010.
90. Wiggins JF, Ruffino L, Kelnar K, Omotola M, Patrawala L, Brown D and Bader AG: Development of a lung cancer therapeutic based on the tumor suppressor microRNA-34. *Cancer Res* 70: 5923-5930, 2010.
91. Ibrahim AF, Weirauch U, Thomas M, Grünweller A, Hartmann RK and Aigner A: MicroRNA replacement therapy for miR-145 and miR-33a is efficacious in a model of colon carcinoma. *Cancer Res* 71: 5214-5224, 2011.
92. Trang P, Wiggins JF, Daige CL, Cho C, Omotola M, Brown D, Weidhaas JB, Bader AG and Slack FJ: Systemic delivery of tumor suppressor microRNA mimics using a neutral lipid emulsion inhibits lung tumors in mice. *Mol Ther* 19: 1116-1122, 2011.
93. Buechner J, Tømte E, Haug BH, Henriksen JR, Løkke C, Flægstad T and Einvik C: Tumour-suppressor microRNAs let-7 and miR-101 target the proto-oncogene MYCN and inhibit cell proliferation in MYCN-amplified neuroblastoma. *Br J Cancer* 105: 296-303, 2011.
94. Scheibner KA, Teaboldt B, Hauer MC, Chen X, Cherukuri S, Guo Y, Kelley SM, Liu Z, Baer MR, Heimfeld S, *et al*: MiR-27a functions as a tumor suppressor in acute leukemia by regulating 14-3-30. *PLoS One* 7: e50895, 2012.
95. Thomas M, Lange-Grünweller K, Weirauch U, Gutsch D, Aigner A, Grünweller A and Hartmann RK: The proto-oncogene Pim-1 is a target of miR-33a. *Oncogene* 31: 918-928, 2012.
96. Endo H, Muramatsu T, Furuta M, Uzawa N, Pimkhaokham A, Amagasa T, Inazawa J and Kozaki K: Potential of tumor-suppressive miR-596 targeting LGALS3BP as a therapeutic agent in oral cancer. *Carcinogenesis* 34: 560-569, 2013.
97. Wu Y, Crawford M, Mao Y, Lee RJ, Davis IC, Elton TS, Lee LJ and Nana-Sinkam SP: Therapeutic delivery of microRNA-29b by cationic lipoplexes for lung cancer. *Mol Ther Nucleic Acids* 2: e84, 2013.
98. Huang X, Schwind S, Yu B, Santhanam R, Wang H, Hoellerbauer P, Mims A, Klisovic R, Walker AR, Chan KK, *et al*: Targeted delivery of microRNA-29b by transferrin-conjugated anionic lipopolyplex nanoparticles: A novel therapeutic strategy in acute myeloid leukemia. *Clin Cancer Res* 19: 2355-2367, 2013.
99. Liang Z, Ahn J, Guo D, Votaw JR and Shim H: MicroRNA-302 replacement therapy sensitizes breast cancer cells to ionizing radiation. *Pharm Res* 30: 1008-1016, 2013.
100. Møller HG, Rasmussen AP, Andersen HH, Johnsen KB, Henriksen M and Duroux M: A systematic review of microRNA in glioblastoma multiforme: Micro-modulators in the mesenchymal mode of migration and invasion. *Mol Neurobiol* 47: 131-144, 2013.
101. Hershkovitz-Rokah O, Modai S, Pasmanik-Chor M, Toren A, Shomron N, Raanani P, Shpilberg O and Granot G: Restoration of miR-424 suppresses BCR-ABL activity and sensitizes CML cells to imatinib treatment. *Cancer Lett* 360: 245-256, 2015.
102. Lee YM, Lee JY, Ho CC, Hong QS, Yu SL, Tzeng CR, Yang PC and Chen HW: miRNA-34b as a tumor suppressor in estrogen-dependent growth of breast cancer cells. *Breast Cancer Res* 13: R116, 2011.
103. Huang P, Ye B, Yang Y, Shi J and Zhao H: MicroRNA-181 functions as a tumor suppressor in non-small cell lung cancer (NSCLC) by targeting Bcl-2. *Tumour Biol* 36: 3381-3387, 2015.
104. Su R, Lin HS, Zhang XH, Yin XL, Ning HM, Liu B, Zhai PF, Gong JN, Shen C, Song L, *et al*: MiR-181 family: Regulators of myeloid differentiation and acute myeloid leukemia as well as potential therapeutic targets. *Oncogene* 34: 3226-3239, 2015.
105. Bachetti T, Di Zanni E, Ravazzolo R and Ceccherini I: miR-204 mediates post-transcriptional down-regulation of PHOX2B gene expression in neuroblastoma cells. *Biochim Biophys Acta* 1849: 1057-1065, 2015.
106. Fernandez S, Risolino M, Mandia N, Talotta F, Soini Y, Incoronato M, Condorelli G, Banfi S and Verde P: miR-340 inhibits tumor cell proliferation and induces apoptosis by targeting multiple negative regulators of p27 in non-small cell lung cancer. *Oncogene* 34: 3240-3250, 2015.
107. Liu G, Liu Y, Yang Z, Wang J, Li D and Zhang X: Tumor suppressor microRNA-18a regulates tumor proliferation and invasion by targeting TBPL1 in colorectal cancer cells. *Mol Med Rep* 12: 7643-7648, 2015.
108. Xishan Z, Ziying L, Jing D and Gang L: MicroRNA-320a acts as a tumor suppressor by targeting BCR/ABL oncogene in chronic myeloid leukemia. *Sci Rep* 5: 12460, 2015.
109. Zhao Z, Ma X, Sung D, Li M, Kostli A, Lin G, Chen Y, Pertsemliadis A, Hsiao TH and Du L: microRNA-449a functions as a tumor suppressor in neuroblastoma through inducing cell differentiation and cell cycle arrest. *RNA Biol* 12: 538-554, 2015.
110. Kalinowski FC, Brown RA, Ganda C, Giles KM, Epis MR, Horsham J and Leedman PJ: microRNA-7: A tumor suppressor miRNA with therapeutic potential. *Int J Biochem Cell Biol* 54: 312-317, 2014.
111. Gu DN, Huang Q and Tian L: The molecular mechanisms and therapeutic potential of microRNA-7 in cancer. *Expert Opin Ther Targets* 19: 415-426, 2015.
112. Nohata N, Hanazawa T, Enokida H and Seki N: microRNA-1/133a and microRNA-206/133b clusters: Dysregulation and functional roles in human cancers. *Oncotarget* 3: 9-21, 2012.
113. Hudson RS, Yi M, Esposito D, Watkins SK, Hurwitz AA, Yfantis HG, Lee DH, Borin JF, Naslund MJ, Alexander RB, *et al*: MicroRNA-1 is a candidate tumor suppressor and prognostic marker in human prostate cancer. *Nucleic Acids Res* 40: 3689-3703, 2012.
114. Chang YS, Chen WY, Yin JJ, Sheppard-Tillman H, Huang J and Liu YN: EGF receptor promotes prostate cancer bone metastasis by downregulating miR-1 and activating TWIST1. *Cancer Res* 75: 3077-3086, 2015.
115. Zhang H, Cai K, Wang J, Wang X, Cheng K, Shi F, Jiang L, Zhang Y and Dou J: MiR-7, inhibited indirectly by lincRNA HOTAIR, directly inhibits SETDB1 and reverses the EMT of breast cancer stem cells by downregulating the STAT3 pathway. *Stem Cells* 32: 2858-2868, 2014a.
116. Okuda H, Xing F, Pandey PR, Sharma S, Watabe M, Pai SK, Mo YY, Iizumi-Gairani M, Hirota S, Liu Y, *et al*: miR-7 suppresses brain metastasis of breast cancer stem-like cells by modulating KLF4. *Cancer Res* 73: 1434-1444, 2013.

117. Zhou X, Hu Y, Dai L, Wang Y, Zhou J, Wang W, Di W and Qiu L: MicroRNA-7 inhibits tumor metastasis and reverses epithelial-mesenchymal transition through AKT/ERK1/2 inactivation by targeting EGFR in epithelial ovarian cancer. *PLoS One* 9: e96718, 2014.
118. Dangi-Garimella S, Yun J, Eves EM, Newman M, Erkeland SJ, Hammond SM, Minn AJ and Rosner MR: Raf kinase inhibitory protein suppresses a metastasis signalling cascade involving LIN28 and let-7. *EMBO J* 28: 347-358, 2009.
119. Takamizawa J, Konishi H, Yanagisawa K, Tomida S, Osada H, Endoh H, Harano T, Yatabe Y, Nagino M, Nimura Y, *et al*: Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Res* 64: 3753-3756, 2004.
120. Shi XB, Tepper CG and deVere White RW: Cancerous miRNAs and their regulation. *Cell Cycle* 7: 1529-1538, 2008.
121. Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, Labourier E, Reinert KL, Brown D and Slack FJ: RAS is regulated by the let-7 microRNA family. *Cell* 120: 635-647, 2005.
122. Zheng L, Qi T, Yang D, Qi M, Li D, Xiang X, Huang K and Tong Q: microRNA-9 suppresses the proliferation, invasion and metastasis of gastric cancer cells through targeting cyclin D1 and Ets1. *PLoS One* 8: e55719, 2013.
123. Aqeilan RI, Calin GA and Croce CM: miR-15a and miR-16-1 in cancer: Discovery, function and future perspectives. *Cell Death Differ* 17: 215-220, 2010.
124. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, *et al*: Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* 99: 15524-15529, 2002.
125. Pekarsky Y and Croce CM: Role of miR-15/16 in CLL. *Cell Death Differ* 22: 6-11, 2015.
126. Bonci D, Coppola V, Musumeci M, Addario A, Giuffrida R, Memeo L, D'Urso L, Pagliuca A, Biffoni M, Labbaye C, *et al*: The miR-15a-miR-16-1 cluster controls prostate cancer by targeting multiple oncogenic activities. *Nat Med* 14: 1271-1277, 2008.
127. Kang W, Tong JH, Lung RW, Dong Y, Zhao J, Liang Q, Zhang L, Pan Y, Yang W, Pang JC, *et al*: Targeting of YAP1 by microRNA-15a and microRNA-16-1 exerts tumor suppressor function in gastric adenocarcinoma. *Mol Cancer* 14: 52, 2015.
128. Chen F, Chen L, He H, Huang W, Zhang R, Li P, *et al*: Up-regulation of microRNA-16 in glioblastoma inhibits the function of endothelial cells and tumor angiogenesis by targeting Bmi-1. *Anticancer Agents Med Chem*, 2015.
129. Humphreys KJ, McKinnon RA and Michael MZ: miR-18a inhibits CDC42 and plays a tumour suppressor role in colorectal cancer cells. *PLoS One* 9: e112288, 2014.
130. Zoni E, van der Horst G, van de Merbel AF, Chen L, Rane JK, Pelger RC, Collins AT, Visakorpi T, Snaar-Jagalska BE, Maitland NJ, *et al*: miR-25 modulates invasiveness and dissemination of human prostate cancer cells via regulation of α - and β integrin expression. *Cancer Res* 75: 2326-2336, 2015.
131. Sengupta S, den Boon JA, Chen IH, Newton MA, Stanhope SA, Cheng YJ, Chen CJ, Hildesheim A, Sugden B and Ahlquist P: MicroRNA 29c is down-regulated in nasopharyngeal carcinomas, up-regulating mRNAs encoding extracellular matrix proteins. *Proc Natl Acad Sci USA* 105: 5874-5878, 2008.
132. Ugalde AP, Ramsay AJ, de la Rosa J, Varela I, Mariño G, Cadiñanos J, Lu J, Freije JM and López-Otín C: Aging and chronic DNA damage response activate a regulatory pathway involving miR-29 and p53. *EMBO J* 30: 2219-2232, 2011.
133. Garzon R, Heaphy CE, Havelange V, Fabbri M, Volinia S, Tsao T, Zanesi N, Kornblau SM, Marcucci G, Calin GA, *et al*: MicroRNA 29b functions in acute myeloid leukemia. *Blood* 114: 5331-5341, 2009a.
134. Garzon R, Liu S, Fabbri M, Liu Z, Heaphy CE, Callegari E, Schwind S, Pang J, Yu J, Muthusamy N, *et al*: MicroRNA-29b induces global DNA hypomethylation and tumor suppressor gene reexpression in acute myeloid leukemia by targeting directly DNMT3A and 3B and indirectly DNMT1. *Blood* 113: 6411-6418, 2009b.
135. Kapinas K, Kessler CB and Delany AM: miR-29 suppression of osteonectin in osteoblasts: Regulation during differentiation and by canonical Wnt signaling. *J Cell Biochem* 108: 216-224, 2009.
136. Mott JL, Kobayashi S, Bronk SF and Gores GJ: miR-29 regulates Mcl-1 protein expression and apoptosis. *Oncogene* 26: 6133-6140, 2007.
137. Fabbri M, Garzon R, Cimmino A, Liu Z, Zanesi N, Callegari E, Liu S, Alder H, Costinean S, Fernandez-Cymering C, *et al*: MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. *Proc Natl Acad Sci USA* 104: 15805-15810, 2007.
138. Xiong Y, Fang JH, Yun JP, Yang J, Zhang Y, Jia WH and Zhuang SM: Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma. *Hepatology* 51: 836-845, 2010.
139. Filkowski JN, Ilynskyy Y, Tamminga J, Koturbash I, Golubov A, Bagnyukova T, Pogribny IP and Kovalchuk O: Hypomethylation and genome instability in the germline of exposed parents and their progeny is associated with altered miRNA expression. *Carcinogenesis* 31: 1110-1115, 2010.
140. Wang Y, Zhang X, Li H, Yu J and Ren X: The role of miRNA-29 family in cancer. *Eur J Cell Biol* 92: 123-128, 2013.
141. Hu W, Dooley J, Chung SS, Chandramohan D, Cimmino L, Mukherjee S, Mason CE, de Strooper B, Liston A and Park CY: miR-29a maintains mouse hematopoietic stem cell self-renewal by regulating Dnmt3a. *Blood* 125: 2206-2216, 2015.
142. Li L and Wang B: Overexpression of microRNA-30b improves adenovirus-mediated p53 cancer gene therapy for laryngeal carcinoma. *Int J Mol Sci* 15: 19729-19740, 2014.
143. Hou C, Sun B, Jiang Y, Zheng J, Yang N, Ji C, Liang Z, Shi J, Zhang R, Liu Y, *et al*: MicroRNA-31 inhibits lung adenocarcinoma stem-like cells via down-regulation of MET-PI3K-Akt signaling pathway. *Anticancer Agents Med Chem* 16: 501-518, 2016.
144. Valastyan S, Reinhardt F, Benaich N, Calogrias D, Szász AM, Wang ZC, Brock JE, Richardson AL and Weinberg RA: A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. *Cell* 137: 1032-1046, 2009.
145. Sossey-Alaoui K, Downs-Kelly E, Das M, Izem L, Tubbs R and Plow EF: WAVE3, an actin remodeling protein, is regulated by the metastasis suppressor microRNA, miR-31, during the invasion-metastasis cascade. *Int J Cancer* 129: 1331-1343, 2011.
146. Lin Y, Liu AY, Fan C, Zheng H, Li Y, Zhang C, Wu S, Yu D, Huang Z, Liu F, *et al*: MicroRNA-33b inhibits breast cancer metastasis by targeting HMGA2, SALL4 and Twist1. *Sci Rep* 5: 9995, 2015.
147. Xu N, Li Z, Yu Z, Yan F, Liu Y, Lu X and Yang W: MicroRNA-33b suppresses migration and invasion by targeting c-Myc in osteosarcoma cells. *PLoS One* 9: e115300, 2014.
148. He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, Xue W, Zender L, Magnus J, Ridzon D, *et al*: A microRNA component of the p53 tumour suppressor network. *Nature* 447: 1130-1134, 2007.
149. Bommer GT, Gerin I, Feng Y, Kaczorowski AJ, Kuick R, Love RE, Zhai Y, Giordano TJ, Qin ZS, Moore BB, *et al*: p53-mediated activation of miRNA34 candidate tumor-suppressor genes. *Curr Biol* 17: 1298-1307, 2007.
150. Fujita Y, Kojima K, Hamada N, Ohhashi R, Akao Y, Nozawa Y, Deguchi T and Ito M: Effects of miR-34a on cell growth and chemoresistance in prostate cancer PC3 cells. *Biochem Biophys Res Commun* 377: 114-119, 2008.
151. Leucci E, Cocco M, Onnis A, De Falco G, van Cleef P, Bellan C, van Rijk A, Nyagol J, Byakika B, Lazzi S, *et al*: MYC translocation-negative classical Burkitt lymphoma cases: An alternative pathogenetic mechanism involving miRNA deregulation. *J Pathol* 216: 440-450, 2008.
152. Saito Y, Nakaoka T and Saito H: microRNA-34a as a therapeutic agent against human cancer. *J Clin Med* 4: 1951-1959, 2015.
153. Wei JS, Song YK, Durinck S, Chen QR, Cheuk AT, Tsang P, Zhang Q, Thiele CJ, Slack A, Shohet J, *et al*: The MYCN oncogene is a direct target of miR-34a. *Oncogene* 27: 5204-5213, 2008.
154. Yamakuchi M, Ferlito M and Lowenstein CJ: miR-34a repression of SIRT1 regulates apoptosis. *Proc Natl Acad Sci USA* 105: 13421-13426, 2008.
155. Lodygin D, Tarasov V, Epanchintsev A, Berking C, Knyazeva T, Körner H, Knyazev P, Diebold J and Hermeking H: Inactivation of miR-34a by aberrant CpG methylation in multiple types of cancer. *Cell Cycle* 7: 2591-2600, 2008.
156. Yang S, Li Y, Gao J, Zhang T, Li S, Luo A, Chen H, Ding F, Wang X and Liu Z: MicroRNA-34 suppresses breast cancer invasion and metastasis by directly targeting Fra-1. *Oncogene* 32: 4294-4303, 2013.
157. Yang P, Li QJ, Feng Y, Zhang Y, Markowitz GJ, Ning S, Deng Y, Zhao J, Jiang S, Yuan Y, *et al*: TGF- β -miR-34a-CCL22 signaling-induced Treg cell recruitment promotes venous metastases of HBV-positive hepatocellular carcinoma. *Cancer Cell* 22: 291-303, 2012.

158. Liu C, Kelnar K, Liu B, Chen X, Calhoun-Davis T, Li H, Patrawala L, Yan H, Jeter C, Honorio S, *et al*: The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44. *Nat Med* 17: 211-215, 2011.
159. Krzeszinski JY, Wei W, Huynh H, Jin Z, Wang X, Chang TC, Xie XJ, He L, Mangala LS, Lopez-Berestein G, *et al*: miR-34a blocks osteoporosis and bone metastasis by inhibiting osteoclastogenesis and Tgif2. *Nature* 512: 431-435, 2014.
160. Wang LG, Ni Y, Su BH, Mu XR, Shen HC and Du JJ: MicroRNA-34b functions as a tumor suppressor and acts as a nodal point in the feedback loop with Met. *Int J Oncol* 42: 957-962, 2013.
161. Yu Z, Kim J, He L, Creighton CJ, Gunaratne PH, Hawkins SM and Matzuk MM: Functional analysis of miR-34c as a putative tumor suppressor in high-grade serous ovarian cancer. *Biol Reprod* 91: 113, 2014.
162. Liu XY, Liu ZJ, He H, Zhang C and Wang YL: MicroRNA-101-3p suppresses cell proliferation, invasion and enhances chemotherapeutic sensitivity in salivary gland adenoid cystic carcinoma by targeting Pim-1. *Am J Cancer Res* 5: 3015-3029, 2015.
163. Tsai WC, Hsu SD, Hsu CS, Lai TC, Chen SJ, Shen R, Huang Y, Chen HC, Lee CH, Tsai TF, *et al*: MicroRNA-122 plays a critical role in liver homeostasis and hepatocarcinogenesis. *J Clin Invest* 122: 2884-2897, 2012.
164. Taniguchi K, Sugito N, Kumazaki M, Shinohara H, Yamada N, Nakagawa Y, Ito Y, Otsuki Y, Uno B, Uchiyama K, *et al*: MicroRNA-124 inhibits cancer cell growth through PTB1/PKM1/PKM2 feedback cascade in colorectal cancer. *Cancer Lett* 363: 17-27, 2015.
165. Huang TC, Chang HY, Chen CY, Wu PY, Lee H, Liao YF, Hsu WM, Huang HC and Juan HF: Silencing of miR-124 induces neuroblastoma SK-N-SH cell differentiation, cell cycle arrest and apoptosis through promoting AHR. *FEBS Lett* 585: 3582-3586, 2011.
166. Kato T, Enomoto A, Watanabe T, Haga H, Ishida S, Kondo Y, Furukawa K, Urano T, Mii S, Weng L, *et al*: TRIM27/MRTF-B-dependent integrin $\beta 1$ expression defines leading cells in cancer cell collectives. *Cell Rep* 7: 1156-1167, 2014.
167. Zheng F, Liao YJ, Cai MY, Liu YH, Liu TH, Chen SP, Bian XW, Guan XY, Lin MC, Zeng YX, *et al*: The putative tumour suppressor microRNA-124 modulates hepatocellular carcinoma cell aggressiveness by repressing ROCK2 and EZH2. *Gut* 61: 278-289, 2012.
168. Wang X, Wu Q, Xu B, Wang P, Fan W, Cai Y, Gu X and Meng F: miR-124 exerts tumor suppressive functions on the cell proliferation, motility and angiogenesis of bladder cancer by fine-tuning UHRF1. *FEBS J* 282: 4376-4388, 2015.
169. Zhang C, Hu Y, Wan J and He H: MicroRNA-124 suppresses the migration and invasion of osteosarcoma cells via targeting ROR2-mediated non-canonical Wnt signaling. *Oncol Rep* 34: 2195-2201, 2015.
170. Sun Y, Ai X, Shen S and Lu S: NF- κ B-mediated miR-124 suppresses metastasis of non-small-cell lung cancer by targeting MYO10. *Oncotarget* 6: 8244-8254, 2015a.
171. Sun Y, Luo ZM, Guo XM, Su DF and Liu X: An updated role of microRNA-124 in central nervous system disorders: A review. *Front Cell Neurosci* 9: 193, 2015b.
172. Chen Z, Liu S, Tian L, Wu M, Ai F, Tang W, Zhao L, Ding J, Zhang L and Tang A: miR-124 and miR-506 inhibit colorectal cancer progression by targeting DNMT3B and DNMT1. *Oncotarget* 6: 38139-38150, 2015.
173. Zhang Y, Li H, Han J and Zhang Y: Down-regulation of microRNA-124 is correlated with tumor metastasis and poor prognosis in patients with lung cancer. *Int J Clin Exp Pathol* 8: 1967-1972, 2015.
174. Cowden Dahl KD, Dahl R, Kruichak JN, Hudson LG: The epidermal growth factor receptor responsive miR-125a represses mesenchymal morphology in ovarian cancer cells. *Neoplasia* 11: 1208-1215, 2009.
175. Fan Z, Cui H, Xu X, Lin Z, Zhang X, Kang L, Han B, Meng J, Yan Z, Yan X, *et al*: MiR-125a suppresses tumor growth, invasion and metastasis in cervical cancer by targeting STAT3. *Oncotarget* 6: 25266-25280, 2015.
176. Sun Y, Bai Y, Zhang F, Wang Y, Guo Y and Guo L: miR-126 inhibits non-small cell lung cancer cells proliferation by targeting EGFL7. *Biochem Biophys Res Commun* 391: 1483-1489, 2010.
177. Xiong Y, Kotian S, Zeiger MA, Zhang L and Kebebew E: miR-126-3p inhibits thyroid cancer cell growth and metastasis, and is associated with aggressive thyroid cancer. *PLoS One* 10: e0130496, 2015.
178. Wang CZ, Yuan P and Li Y: MiR-126 regulated breast cancer cell invasion by targeting ADAM9. *Int J Clin Exp Pathol* 8: 6547-6553, 2015.
179. Wen Q, Zhao J, Bai L, Wang T, Zhang H and Ma Q: miR-126 inhibits papillary thyroid carcinoma growth by targeting LRP6. *Oncol Rep* 34: 2202-2210, 2015.
180. Jiang L, He A, Zhang Q and Tao C: miR-126 inhibits cell growth, invasion, and migration of osteosarcoma cells by down-regulating ADAM-9. *Tumour Biol* 35: 12645-12654, 2014.
181. Du C, Lv Z, Cao L, Ding C, Gyabaah OA, Xie H, Zhou L, Wu J and Zheng S: MiR-126-3p suppresses tumor metastasis and angiogenesis of hepatocellular carcinoma by targeting LRP6 and PIK3R2. *J Transl Med* 12: 259, 2014.
182. Zhang Y, Wang X, Xu B, Wang B, Wang Z, Liang Y, Zhou J, Hu J and Jiang B: Epigenetic silencing of miR-126 contributes to tumor invasion and angiogenesis in colorectal cancer. *Oncol Rep* 30: 1976-1984, 2013.
183. Png KJ, Halberg N, Yoshida M and Tavazoie SF: A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells. *Nature* 481: 190-194, 2011.
184. Shi ZM, Wang J, Yan Z, You YP, Li CY, Qian X, Yin Y, Zhao P, Wang YY, Wang XF, *et al*: MiR-128 inhibits tumor growth and angiogenesis by targeting p70S6K1. *PLoS One* 7: e32709, 2012.
185. Wuchty S, Arjona D, Li A, Kotliarov Y, Walling J, Ahn S, Zhang A, Maric D, Anolik R, Zenklusen JC, *et al*: Prediction of associations between microRNAs and gene expression in glioma biology. *PLoS One* 6: e14681, 2011.
186. Zhang Y, Chao T, Li R, Liu W, Chen Y, Yan X, Gong Y, Yin B, Liu W, Qiang B, *et al*: MicroRNA-128 inhibits glioma cells proliferation by targeting transcription factor E2F3a. *J Mol Med Berl* 87: 43-51, 2009.
187. Huang CY, Huang XP, Zhu JY, Chen ZG, Li XJ, Zhang XH, Huang S, He JB, Lian F, Zhao YN, *et al*: miR-128-3p suppresses hepatocellular carcinoma proliferation by regulating PIK3R1 and is correlated with the prognosis of HCC patients. *Oncol Rep* 33: 2889-2898, 2015.
188. Kano M, Seki N, Kikkawa N, Fujimura L, Hoshino I, Akutsu Y, Chiyomaru T, Enokida H, Nakagawa M and Matsubara H: miR-145, miR-133a and miR-133b: Tumor-suppressive miRNAs target FSCN1 in esophageal squamous cell carcinoma. *Int J Cancer* 127: 2804-2814, 2010.
189. Kroiss A, Vincent S, Decaussin-Petrucci M, Meugnier E, Viallet J, Ruffion A, Chalmel F, Samarut J and Allioi N: Androgen-regulated microRNA-135a decreases prostate cancer cell migration and invasion through downregulating ROCK1 and ROCK2. *Oncogene* 34: 2846-2855, 2015.
190. Liang L, Li X, Zhang X, Lv Z, He G, Zhao W, Ren X, Li Y, Bian X, Liao W, *et al*: MicroRNA-137, an HMGAl target, suppresses colorectal cancer cell invasion and metastasis in mice by directly targeting FMNL2. *Gastroenterology* 144: 624-635.e4, 2013.
191. Xia H, Sun S, Wang B, Wang T, Liang C, Li G, Huang C, Qi D and Chu X: miR-143 inhibits NSCLC cell growth and metastasis by targeting Limk1. *Int J Mol Sci* 15: 11973-11983, 2014.
192. Gao P, Xing AY, Zhou GY, Zhang TG, Zhang JP, Gao C, Li H and Shi DB: The molecular mechanism of microRNA-145 to suppress invasion-metastasis cascade in gastric cancer. *Oncogene* 32: 491-501, 2013.
193. Zhang H, Pu J, Qi T, Qi M, Yang C, Li S, Huang K, Zheng L and Tong Q: MicroRNA-145 inhibits the growth, invasion, metastasis and angiogenesis of neuroblastoma cells through targeting hypoxia-inducible factor 2 alpha. *Oncogene* 33: 387-397, 2014.
194. Bhaumik D, Scott GK, Schokrpur S, Patil CK, Campisi J and Benz CC: Expression of microRNA-146 suppresses NF-kappaB activity with reduction of metastatic potential in breast cancer cells. *Oncogene* 27: 5643-5647, 2008.
195. Lin SL, Chiang A, Chang D and Ying SY: Loss of miR-146a function in hormone-refractory prostate cancer. *RNA* 14: 417-424, 2008.
196. Zhang JP, Zeng C, Xu L, Gong J, Fang JH and Zhuang SM: MicroRNA-148a suppresses the epithelial-mesenchymal transition and metastasis of hepatoma cells by targeting Met/Snail signaling. *Oncogene* 33: 4069-4076, 2014.
197. Cimino D, De Pittà C, Orso F, Zampini M, Casara S, Penna E, Quaglino E, Forni M, Damasco C, Pinatelli E, *et al*: miR148b is a major coordinator of breast cancer progression in a relapse-associated microRNA signature by targeting ITGA5, ROCK1, PIK3CA, NRAS, and CSF1. *FASEB J* 27: 1223-1235, 2013.
198. Bischoff A, Huck B, Keller B, Strotbek M, Schmid S, Boerries M, Busch H, Müller D and Olayioye MA: miR149 functions as a tumor suppressor by controlling breast epithelial cell migration and invasion. *Cancer Res* 74: 5256-5265, 2014.

199. Visone R, Veronese A, Rassenti LZ, Balatti V, Pearl DK, Acunzo M, Volinia S, Taccioli C, Kipps TJ and Croce CM: miR-181b is a biomarker of disease progression in chronic lymphocytic leukemia. *Blood* 118: 3072-3079, 2011.
200. Kourri FM, Hurley LA, Daniel WL, Day ES, Hua Y, Hao L, Peng CY, Merkel TJ, Queisser MA, Kyner C, *et al*: miR-182 integrates apoptosis, growth, and differentiation programs in glioblastoma. *Genes Dev* 29: 732-745, 2015.
201. Leivonen SK, Rokka A, Ostling P, Kohonen P, Corthals GL, Kallioniemi O and Perälä M: Identification of miR-193b targets in breast cancer cells and systems biological analysis of their functional impact. *Mol Cell Proteomics* 10: M110.005322, 2011.
202. Yang H, Liu P, Zhang J, Peng X, Lu Z, Yu S, Meng Y, Tong WM and Chen J: Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. *Oncogene*: Nov 9, 2015 (Epub ahead of print).
203. Tan S, Li R, Ding K, Lobie PE and Zhu T: miR-198 inhibits migration and invasion of hepatocellular carcinoma cells by targeting the HGF/c-MET pathway. *FEBS Lett* 585: 2229-2234, 2011.
204. Bao W, Wang HH, Tian FJ, He XY, Qiu MT, Wang JY, Zhang HJ, Wang LH and Wan XP: A TrkB-STAT3-miR-204-5p regulatory circuitry controls proliferation and invasion of endometrial carcinoma cells. *Mol Cancer* 12: 155, 2013.
205. Xia Z, Liu F, Zhang J and Liu L: Decreased expression of MiRNA-204-5p contributes to glioma progression and promotes glioma cell growth, migration and invasion. *PLoS One* 10: e0132399, 2015.
206. Gandellini P, Folini M, Longoni N, Pennati M, Binda M, Colecchia M, Salvioni R, Supino R, Moretti R, Limonta P, *et al*: miR-205 exerts tumor-suppressive functions in human prostate through down-regulation of protein kinase Cepsilon. *Cancer Res* 69: 2287-2295, 2009.
207. Chen QY, Jiao DM, Yan L, Wu YQ, Hu HZ, Song J, Yan J, Wu LJ, Xu LQ and Shi JG: Comprehensive gene and microRNA expression profiling reveals miR-206 inhibits MET in lung cancer metastasis. *Mol Biosyst* 11: 2290-2302, 2015.
208. Chen DL, Wang ZQ, Zeng ZL, Wu WJ, Zhang DS, Luo HY, Wang F, Qiu MZ, Wang DS, Ren C, *et al*: Identification of microRNA-214 as a negative regulator of colorectal cancer liver metastasis by way of regulation of fibroblast growth factor receptor 1 expression. *Hepatology* 60: 598-609, 2014.
209. Tie J, Pan Y, Zhao L, Wu K, Liu J, Sun S, Guo X, Wang B, Gang Y, Zhang Y, *et al*: MiR-218 inhibits invasion and metastasis of gastric cancer by targeting the Robo1 receptor. *PLoS Genet* 6: e1000879, 2010.
210. Wei JJ, Wu X, Peng Y, Shi G, Basturk O, Yang X, Daniels G, Osman I, Ouyang J, Hernando E, *et al*: Regulation of HMGAI expression by microRNA-296 affects prostate cancer growth and invasion. *Clin Cancer Res* 17: 1297-1305, 2011.
211. Wang L, Yao J, Shi X, Hu L, Li Z, Song T and Huang C: MicroRNA-302b suppresses cell proliferation by targeting EGFR in human hepatocellular carcinoma SMMC-7721 cells. *BMC Cancer* 13: 448, 2013.
212. Tavazoie SF, Alarcón C, Oskarsson T, Padua D, Wang Q, Bos PD, Gerald WL and Massagué J: Endogenous human microRNAs that suppress breast cancer metastasis. *Nature* 451: 147-152, 2008.
213. Hurst DR, Edmonds MD and Welch DR: Metastamir: The field of metastasis-regulatory microRNA is spreading. *Cancer Res* 69: 7495-7498, 2009.
214. Li KK, Pang JC, Lau KM, Zhou L, Mao Y, Wang Y, Poon WS and Ng HK: MiR-383 is downregulated in medulloblastoma and targets peroxiredoxin 3 (PRDX3). *Brain Pathol* 23: 413-425, 2013.
215. Bou Kheir T, Futoma-Kazmierczak E, Jacobsen A, Krogh A, Bardram L, Hother C, Grønbaek K, Federspiel B, Lund AH and Friis-Hansen L: miR-449 inhibits cell proliferation and is down-regulated in gastric cancer. *Mol Cancer* 10: 29, 2011.
216. Luo W, Huang B, Li Z, Li H, Sun L, Zhang Q, Qiu X and Wang E: MicroRNA-449a is downregulated in non-small cell lung cancer and inhibits migration and invasion by targeting c-Met. *PLoS One* 8: e64759, 2013.
217. Okamoto K, Ishiguro T, Midorikawa Y, Ohata H, Izumiya M, Tsuchiya N, Sato A, Sakai H and Nakagama H: miR-493 induction during carcinogenesis blocks metastatic settlement of colon cancer cells in liver. *EMBO J* 31: 1752-1763, 2012.
218. Gu Y, Cheng Y, Song Y, Zhang Z, Deng M, Wang C, Zheng G and He Z: MicroRNA-493 suppresses tumor growth, invasion and metastasis of lung cancer by regulating E2F1. *PLoS One* 9: e102602, 2014.
219. Sakai HI, Sato A, Aihara Y, Ikarashi Y, Midorikawa Y, Kracht M, Nakagama H and Okamoto K: MKK7 mediates miR-493-dependent suppression of liver metastasis of colon cancer cells. *Cancer Sci* 105: 425-430, 2014.
220. Kikkawa N, Kinoshita T, Nohata N, Hanazawa T, Yamamoto N, Fukumoto I, Chiyomaru T, Enokida H, Nakagawa M, Okamoto Y, *et al*: microRNA-504 inhibits cancer cell proliferation via targeting CDK6 in hypopharyngeal squamous cell carcinoma. *Int J Oncol* 44: 2085-2092, 2014.
221. Keklikoglou I, Koerner C, Schmidt C, Zhang JD, Heckmann D, Shavinskaya A, Allgayer H, Gückel B, Fehm T, Schneeweiss A, *et al*: MicroRNA-520/373 family functions as a tumor suppressor in estrogen receptor negative breast cancer by targeting NF-κB and TGF-β signaling pathways. *Oncogene* 31: 4150-4163, 2012.
222. Song B, Ji W, Guo S, Liu A, Jing W, Shao C, Li G and Jin G: miR-545 inhibited pancreatic ductal adenocarcinoma growth by targeting RIG-I. *FEBS Lett* 588: 4375-4381, 2014.
223. Bowen D, Zhe W, Xin Z, Shipeng F, Guoxin W, Jianxing H and Zhang B: MicroRNA-545 suppresses cell proliferation by targeting cyclin D1 and CDK4 in lung cancer cells. *PLoS* 9: 88022, 2014.
224. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, Iorio MV, Visone R, Sever NI, Fabbri M, *et al*: A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *N Engl J Med* 353: 1793-1801, 2005.
225. Esquela-Kerscher A and Slack FJ: Oncomirs - microRNAs with a role in cancer. *Nat Rev Cancer* 6: 259-269, 2006.
226. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, *et al*: MicroRNA gene expression deregulation in human breast cancer. *Cancer Res* 65: 7065-7070, 2005.
227. Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, Taccioli C, Volinia S, Liu CG, Alder H, *et al*: MicroRNA signatures in human ovarian cancer. *Cancer Res* 67: 8699-8707, 2007.
228. Porkka KP, Pfeiffer MJ, Waltering KK, Vessella RL, Tammela TL and Visakorpi T: MicroRNA expression profiling in prostate cancer. *Cancer Res* 67: 6130-6135, 2007.
229. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST and Patel T: MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology* 133: 647-658, 2007.
230. Zhu S, Si ML, Wu H and Mo YY: MicroRNA-21 targets the tumor suppressor gene tropomyosin 1 (TPM1). *J Biol Chem* 282: 14328-14336, 2007.
231. Frankel LB, Christoffersen NR, Jacobsen A, Lindow M, Krogh A and Lund AH: Programmed cell death 4 (PDCD4) is an important functional target of the microRNA miR-21 in breast cancer cells. *J Biol Chem* 283: 1026-1033, 2008.
232. Garzon R, Volinia S, Liu CG, Fernandez-Cymering C, Palumbo T, Pichiorri F, Fabbri M, Coombes K, Alder H, Nakamura T, *et al*: MicroRNA signatures associated with cytogenetics and prognosis in acute myeloid leukemia. *Blood* 111: 3183-3189, 2008.
233. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, *et al*: A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc Natl Acad Sci USA* 103: 2257-2261, 2006.
234. White NM, Fatoohi E, Metias M, Jung K, Stephan C and Yousef GM: Metastamirs: A stepping stone towards improved cancer management. *Nat Rev Clin Oncol* 8: 75-84, 2011.
235. Zhou L, Liu F, Wang X and Ouyang G: The roles of microRNAs in the regulation of tumor metastasis. *Cell Biosci* 5: 32, 2015.
236. Wang XH, Cai P, Wang MH and Wang Z: microRNA 25 promotes osteosarcoma cell proliferation by targeting the cell cycle inhibitor p27. *Mol Med Rep* 10: 855-859, 2014.
237. Siu MK, Tsai YC, Chang YS, Yin JJ, Suau F, Chen WY and Liu YN: Transforming growth factor-β promotes prostate bone metastasis through induction of microRNA-96 and activation of the mTOR pathway. *Oncogene* 34: 4767-4776, 2015.
238. Xia X, Li Y, Wang W, Tang F, Tan J, Sun L, Li Q, Sun L, Tang B and He S: MicroRNA-1908 functions as a glioblastoma oncogene by suppressing PTEN tumor suppressor pathway. *Mol Cancer* 14: 154, 2015.
239. Sachdeva M, Mito JK, Lee CL, Zhang M, Li Z, Dodd RD, Cason D, Luo L, Ma Y, Van Mater D, *et al*: MicroRNA-182 drives metastasis of primary sarcomas by targeting multiple genes. *J Clin Invest* 124: 4305-4319, 2014.

240. Tian Y, Luo A, Cai Y, Su Q, Ding F, Chen H and Liu Z: MicroRNA-10b promotes migration and invasion through KLF4 in human esophageal cancer cell lines. *J Biol Chem* 285: 7986-7994, 2010.
241. Wang YY, Ye ZY, Zhao ZS, Li L, Wang YX, Tao HQ, Wang HJ and He XJ: Clinicopathologic significance of miR-10b expression in gastric carcinoma. *Hum Pathol* 44: 1278-1285, 2013.
242. Chan JA, Krichevsky AM and Kosik KS: MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res* 65: 6029-6033, 2005.
243. Liu W, Zabornyk O, Wang H, Shiao YH, Nickerson ML, Khalil S, Anderson LM, Perantoni AO and Phang JM: miR-23b targets proline oxidase, a novel tumor suppressor protein in renal cancer. *Oncogene* 29: 4914-4924, 2010.
244. Fletcher CE, Dart DA, Sita-Lumsden A, Cheng H, Rennie PS and Bevan CL: Androgen-regulated processing of the oncomir miR-27a, which targets Prohibitin in prostate cancer. *Hum Mol Genet* 21: 3112-3127, 2012.
245. Ng WL, Yan D, Zhang X, Mo YY and Wang Y: Over-expression of miR-100 is responsible for the low-expression of ATM in the human glioma cell line: M059J. *DNA Repair (Amst)* 9: 1170-1175, 2010.
246. Zheng YS, Zhang H, Zhang XJ, Feng DD, Luo XQ, Zeng CW, Lin KY, Zhou H, Qu LH, Zhang P, *et al*: MiR-100 regulates cell differentiation and survival by targeting RBSP3, a phosphatase-like tumor suppressor in acute myeloid leukemia. *Oncogene* 31: 80-92, 2012.
247. Knackmuss U, Lindner SE, Anechych T, Kotkamp B, Knust Z, Villunger A and Herzog S: MAP3K11 is a tumor suppressor targeted by the oncomir miR-125b in early B cells. *Cell Death Differ* 23: 242-252, 2016.
248. Park JK, Henry JC, Jiang J, Esau C, Gusev Y, Lerner MR, Postier RG, Brackett DJ and Schmittgen TD: miR-132 and miR-212 are increased in pancreatic cancer and target the retinoblastoma tumor suppressor. *Biochem Biophys Res Commun* 406: 518-523, 2011.
249. Kong W, He L, Coppola M, Guo J, Esposito NN, Coppola D and Cheng JQ: MicroRNA-155 regulates cell survival, growth, and chemosensitivity by targeting FOXO3a in breast cancer. *J Biol Chem* 285: 17869-17879, 2010.
250. Jiang S, Zhang HW, Lu MH, He XH, Li Y, Gu H, Liu MF and Wang ED: MicroRNA-155 functions as an Oncomir in breast cancer by targeting the suppressor of cytokine signaling 1 gene. *Cancer Res* 70: 3119-3127, 2010.
251. Czyzyk-Krzeska MF and Zhang X: MiR-155 at the heart of oncogenic pathways. *Oncogene* 33: 677-678, 2014.
252. Wang J and Wu J: Role of miR-155 in breast cancer. *Front Biosci (Landmark Ed)* 17: 2350-2355, 2012.
253. Ling N, Gu J, Lei Z, Li M, Zhao J, Zhang HT and Li X: microRNA-155 regulates cell proliferation and invasion by targeting FOXO3a in glioma. *Oncol Rep* 30: 2111-2118, 2013.
254. Musilova K and Mraz M: MicroRNAs in B-cell lymphomas: How a complex biology gets more complex. *Leukemia* 29: 1004-1017, 2015.
255. Fontana L, Fiori ME, Albini S, Cifaldi L, Giovinazzi S, Forloni M, Boldrini R, Donfrancesco A, Federici V, Giacomini P, *et al*: AntagomiR-17-5p abolishes the growth of therapy-resistant neuroblastoma through p21 and BIM. *PLoS One* 3: e2236, 2008.
256. Segura MF, Hanniford D, Menendez S, Reavie L, Zou X, Alvarez-Diaz S, Zakrzewski J, Blochin E, Rose A, Bogunovic D, *et al*: Aberrant miR-182 expression promotes melanoma metastasis by repressing FOXO3 and microphthalmia-associated transcription factor. *Proc Natl Acad Sci USA* 106: 1814-1819, 2009.
257. Yang H, Kong W, He L, Zhao JJ, O'Donnell JD, Wang J, Wenham RM, Coppola D, Kruk PA, Nicosia SV, *et al*: MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN. *Cancer Res* 68: 425-433, 2008.
258. Zhang CZ, Zhang JX, Zhang AL, Shi ZD, Han L, Jia ZF, Yang WD, Wang GX, Jiang T, You YP, *et al*: MiR-221 and miR-222 target PUMA to induce cell survival in glioblastoma. *Mol Cancer* 9: 229, 2010.
259. Garofalo M, Quintavalle C, Romano G, Croce CM and Condorelli G: miR221/222 in cancer: Their role in tumor progression and response to therapy. *Curr Mol Med* 12: 27-33, 2012.
260. Quintavalle C, Garofalo M, Zanca C, Romano G, Iaboni M, del Basso De Caro M, Martinez-Montero JC, Incoronato M, Nuovo G, Croce CM, *et al*: miR-221/222 overexpression in human glioblastoma increases invasiveness by targeting the protein phosphate PTP μ . *Oncogene* 31: 858-868, 2012.
261. Chen WX, Hu Q, Qiu MT, Zhong SL, Xu JJ, Tang JH and Zhao JH: miR-221/222: Promising biomarkers for breast cancer. *Tumour Biol* 34: 1361-1370, 2013.
262. Matsuzaki J and Suzuki H: Role of MicroRNAs-221/222 in digestive systems. *J Clin Med* 4: 1566-1577, 2015.
263. Würdinger T, Tannous BA, Saydam O, Skog J, Grau S, Soutschek J, Weissleder R, Breakefield XO and Krichevsky AM: miR-296 regulates growth factor receptor overexpression in angiogenic endothelial cells. *Cancer Cell* 14: 382-393, 2008.
264. Shi W, Gerster K, Alajez NM, Tsang J, Waldron L, Pintilie M, Hui AB, Sykes J, P'ng C, Miller N, *et al*: MicroRNA-301 mediates proliferation and invasion in human breast cancer. *Cancer Res* 71: 2926-2937, 2011.
265. Voorhoeve PM, le Sage C, Schrier M, Gillis AJ, Stoop H, Nagel R, Liu YP, van Duijse J, Drost J, Griekspoor A, *et al*: A genetic screen implicates miRNA-372 and miRNA-373 as oncogenes in testicular germ cell tumors. *Adv Exp Med Biol* 604: 17-46, 2007.
266. Xu Y, Jin J, Liu Y, Huang Z, Deng Y, You T, Zhou T, Si J and Zhuo W: Snail-regulated MiR-375 inhibits migration and invasion of gastric cancer cells by targeting JAK2. *PLoS One* 9: e9516, 2014.
267. Lee DY, Deng Z, Wang CH and Yang BB: MicroRNA-378 promotes cell survival, tumor growth, and angiogenesis by targeting SuFu and Fus-1 expression. *Proc Natl Acad Sci USA* 104: 20350-20355, 2007.
268. Tu K, Liu Z, Yao B, Han S and Yang W: MicroRNA-519a promotes tumor growth by targeting PTEN/PI3K/AKT signaling in hepatocellular carcinoma. *Int J Oncol* 48: 965-974, 2016.
269. Shao J, Cao J, Liu Y, Mei H, Zhang Y and Xu W: MicroRNA-519a promotes proliferation and inhibits apoptosis of hepatocellular carcinoma cells by targeting FOXF2. *FEBS Open Bio* 5: 893-899, 2015.
270. Ward A, Shukla K, Balwierz A, Soons Z, König R, Sahin O and Wiemann S: MicroRNA-519a is a novel oncomir conferring tamoxifen resistance by targeting a network of tumour-suppressor genes in ER⁺ breast cancer. *J Pathol* 233: 368-379, 2014.
271. Tsang WP, Ng EK, Ng SS, Jin H, Yu J, Sung JJ and Kwok TT: Oncofetal H19-derived miR-675 regulates tumor suppressor RB in human colorectal cancer. *Carcinogenesis* 31: 350-358, 2010.
272. Ma L, Young J, Prabhala H, Pan E, Mestdagh P, Muth D, Teruya-Feldstein J, Reinhardt F, Onder TT, Valastyan S, *et al*: miR-9, a MYC/MYCN-activated microRNA, regulates E-cadherin and cancer metastasis. *Nat Cell Biol* 12: 247-256, 2010.
273. Chen D, Sun Y, Wei Y, Zhang P, Rezaeian AH, Teruya-Feldstein J, Gupta S, Liang H, Lin HK, Hung MC, *et al*: LIFR is a breast cancer metastasis suppressor upstream of the Hippo-YAP pathway and a prognostic marker. *Nat Med* 18: 1511-1517, 2012.
274. White RA, Neiman JM, Reddi A, Han G, Birlea S, Mitra D, Dionne L, Fernandez P, Murao K, Bian L, *et al*: Epithelial stem cell mutations that promote squamous cell carcinoma metastasis. *J Clin Invest* 123: 4390-4404, 2013.
275. Ma L, Teruya-Feldstein J and Weinberg RA: Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. *Nature* 449: 682-688, 2007.
276. Lin J, Teo S, Lam DH, Jeyaseelan K and Wang S: MicroRNA-10b pleiotropically regulates invasion, angiogenicity and apoptosis of tumor cells resembling mesenchymal subtype of glioblastoma multiforme. *Cell Death Dis* 3: e398, 2012.
277. Zhang WL, Zhang JH, Wu XZ, Yan T and Lv W: miR-15b promotes epithelial-mesenchymal transition by inhibiting SMURF2 in pancreatic cancer. *Int J Oncol* 47: 1043-1053, 2015.
278. Wu Q, Yang Z, An Y, Hu H, Yin J, Zhang P, Nie Y, Wu K, Shi Y and Fan D: MiR-19a/b modulate the metastasis of gastric cancer cells by targeting the tumour suppressor MXD1. *Cell Death Dis* 5: e1144, 2014.
279. Chang Y, Liu C, Yang J, Liu G, Feng F, Tang J, Hu L, Li L, Jiang F, Chen C, *et al*: MiR-20a triggers metastasis of gallbladder carcinoma. *J Hepatol* 59: 518-527, 2013.
280. Zhao S, Yao D, Chen J, Ding N and Ren F: MiR-20a promotes cervical cancer proliferation and metastasis in vitro and in vivo. *PLoS One* 10: e0120905, 2015.
281. Dean ZS, Riahi R and Wong PK: Spatiotemporal dynamics of microRNA during epithelial collective cell migration. *Biomaterials* 37: 156-163, 2015.
282. Peacock O, Lee AC, Cameron F, Tarbox R, Vafadar-Isfahani N, Tufarelli C and Lund JN: Inflammation and MiR-21 pathways functionally interact to downregulate PDCD4 in colorectal cancer. *PLoS One* 9: e110267, 2014.

283. Xu J, Zhang W, Lv Q and Zhu D: Overexpression of miR-21 promotes the proliferation and migration of cervical cancer cells via the inhibition of PTEN. *Oncol Rep* 33: 3108-3116, 2015.
284. Asangani IA, Rasheed SA, Nikolova DA, Leupold JH, Colburn NH, Post S and Allgayer H: MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer. *Oncogene* 27: 2128-2136, 2008.
285. Melnik BC: MiR-21: An environmental driver of malignant melanoma? *J Transl Med* 13: 202, 2015.
286. Zhou W, Fong MY, Min Y, Somlo G, Liu L, Palomares MR, Yu Y, Chow A, O'Connor ST, Chin AR, *et al*: Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. *Cancer Cell* 25: 501-515, 2014.
287. Fong MY, Zhou W, Liu L, Alontaga AY, Chandra M, Ashby J, Chow A, O'Connor ST, Li S, Chin AR, *et al*: Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis. *Nat Cell Biol* 17: 183-194, 2015.
288. Lin CW, Chang YL, Chang YC, Lin JC, Chen CC, Pan SH, Wu CT, Chen HY, Yang SC, Hong TM, *et al*: MicroRNA-135b promotes lung cancer metastasis by regulating multiple targets in the Hippo pathway and LZTS1. *Nat Commun* 4: 1877, 2013.
289. Taylor MA, Sossey-Alaoui K, Thompson CL, Danielpour D and Schiemann WP: TGF- β upregulates miR-181a expression to promote breast cancer metastasis. *J Clin Invest* 123: 150-163, 2013.
290. Qiu Y, Luo X, Kan T, Zhang Y, Yu W, Wei Y, Shen N, Yi B and Jiang X: TGF- β upregulates miR-182 expression to promote gallbladder cancer metastasis by targeting CADM1. *Mol Biosyst* 10: 679-685, 2014.
291. Ren LH, Chen WX, Li S, He XY, Zhang ZM, Li M, Cao RS, Hao B, Zhang HJ, Qiu HQ, *et al*: MicroRNA-183 promotes proliferation and invasion in oesophageal squamous cell carcinoma by targeting programmed cell death 4. *Br J Cancer* 111: 2003-2013, 2014.
292. Korpala M, Lee ES, Hu G and Kang Y: The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. *J Biol Chem* 283: 14910-14914, 2008.
293. Korpala M, Ell BJ, Buffa FM, Ibrahim T, Blanco MA, Celià-Terrassa T, Mercatali L, Khan Z, Goodarzi H, Hua Y, *et al*: Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization. *Nat Med* 17: 1101-1108, 2011.
294. Park SM, Gaur AB, Lengyel E and Peter ME: The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. *Genes Dev* 22: 894-907, 2008.
295. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, Vadas MA, Khew-Goodall Y and Goodall GJ: The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. *Nat Cell Biol* 10: 593-601, 2008.
296. Penna E, Orso F, Cimino D, Tenaglia E, Lembo A, Quagliano E, Poliseño L, Haimovic A, Osella-Abate S, De Pittà C, *et al*: microRNA-214 contributes to melanoma tumour progression through suppression of TFAP2C. *EMBO J* 30: 1990-2007, 2011.
297. Penna E, Orso F, Cimino D, Vercellino I, Grassi E, Quagliano E, Turco E and Taverna D: miR-214 coordinates melanoma progression by upregulating ALCAM through TFAP2 and miR-148b downmodulation. *Cancer Res* 73: 4098-4111, 2013.
298. Long H, Wang Z, Chen J, Xiang T, Li Q, Diao X and Zhu B: microRNA-214 promotes epithelial-mesenchymal transition and metastasis in lung adenocarcinoma by targeting the suppressor-of-fused protein (Sufu). *Oncotarget* 6: 38705-38718, 2015.
299. Liu X, Chen Q, Yan J, Wang Y, Zhu C, Chen C, Zhao X, Xu M, Sun Q, Deng R, *et al*: MiRNA-296-3p-ICAM-1 axis promotes metastasis of prostate cancer by possible enhancing survival of natural killer cell-resistant circulating tumour cells. *Cell Death Dis* 4: e928, 2013.
300. Vaira V, Faversani A, Martin NM, Garlick DS, Ferrero S, Nosotti M, Kissil JL, Bosari S and Altieri DC: Regulation of lung cancer metastasis by Klf4-Numb-like signaling. *Cancer Res* 73: 2695-2705, 2013.
301. Ni F, Zhao H, Cui H, Wu Z, Chen L, Hu Z, Guo C, Liu Y, Chen Z, Wang X, *et al*: MicroRNA-362-5p promotes tumor growth and metastasis by targeting CYLD in hepatocellular carcinoma. *Cancer Lett* 356: 809-818, 2015.
302. Chen D, Dang BL, Huang JZ, Chen M, Wu D, Xu ML, Li R and Yan GR: MiR-373 drives the epithelial-to-mesenchymal transition and metastasis via the miR-373-TXNIP-HIF1 α -TWIST signaling axis in breast cancer. *Oncotarget* 6: 32701-32712, 2015.
303. Lu S, Zhu Q, Zhang Y, Song W, Wilson MJ and Liu P: Dual-functions of miR-373 and miR-520c by differentially regulating the activities of MMP2 and MMP9. *J Cell Physiol* 230: 1862-1870, 2015.
304. Glover AR, Zhao JT, Gill AJ, Weiss J, Mugridge N, Kim E, Feeney AL, Ip JC, Reid G, Clarke S, *et al*: MicroRNA-7 as a tumor suppressor and novel therapeutic for adrenocortical carcinoma. *Oncotarget* 6: 36675-36688, 2015.
305. Babae N, Bourajaj M, Liu Y, Van Beijnum JR, Cerisoli F, Scaria PV, Verheul M, Van Berkel MP, Pieters EH, Van Haastert RJ, *et al*: Systemic miRNA-7 delivery inhibits tumor angiogenesis and growth in murine xenograft glioblastoma. *Oncotarget* 5: 6687-6700, 2014.
306. Wang W, Dai LX, Zhang S, Yang Y, Yan N, Fan P, Dai L, Tian HW, Cheng L, Zhang XM, *et al*: Regulation of epidermal growth factor receptor signaling by plasmid-based microRNA-7 inhibits human malignant gliomas growth and metastasis in vivo. *Neoplasia* 60: 274-283, 2013.
307. Cortez MA, Valdecanas D, Zhang X, Zhan Y, Bhardwaj V, Calin GA, Komaki R, Giri DK, Quini CC, Wolfe T, *et al*: Therapeutic delivery of miR-200c enhances radiosensitivity in lung cancer. *Mol Ther* 22: 1494-1503, 2014.
308. Wu X, Liu T, Fang O, Dong W, Zhang F, Leach L, Hu X and Luo Z: MicroRNA-708-5p acts as a therapeutic agent against metastatic lung cancer. *Oncotarget* 7: 2417-2432, 2016.
309. Ge YF, Sun J, Jin CJ, Cao BQ, Jiang ZF and Shao JF: AntagomiR-27a targets FOXO3a in glioblastoma and suppresses U87 cell growth in vitro and in vivo. *Asian Pac J Cancer Prev* 14: 963-968, 2013.
310. Shu M, Zheng X, Wu S, Lu H, Leng T, Zhu W, Zhou Y, Ou Y, Lin X, Lin Y, *et al*: Targeting oncogenic miR-335 inhibits growth and invasion of malignant astrocytoma cells. *Mol Cancer* 10: 59, 2011.
311. Rather MI, Nagashri MN, Swamy SS, Gopinath KS and Kumar A: Oncogenic microRNA-155 down-regulates tumor suppressor CDC73 and promotes oral squamous cell carcinoma cell proliferation: Implications for cancer therapeutics. *J Biol Chem* 288: 608-618, 2013.
312. Haug BH, Henriksen JR, Buechner J, Geerts D, Tømte E, Kogner P, Martinsson T, Flægstad T, Sveinbjørnsson B and Einvik C: MYCN-regulated miRNA-92 inhibits secretion of the tumor suppressor DICKKOPF-3 (DKK3) in neuroblastoma. *Carcinogenesis* 32: 1005-1012, 2011.
313. Tang H, Liu X, Wang Z, She X, Zeng X, Deng M, Liao Q, Guo X, Wang R, Li X, *et al*: Interaction of hsa-miR-381 and glioma suppressor LRRC4 is involved in glioma growth. *Brain Res* 1390: 21-32, 2011.
314. Ma L, Reinhardt F, Pan E, Soutschek J, Bhat B, Marcusson EG, Truya-Feldstein J, Bell GW and Weinberg RA: Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. *Nat Biotechnol* 28: 341-347, 2010.
315. Mercatelli N, Coppola V, Bonci D, Miele F, Costantini A, Guadagnoli M, Bonanno E, Muto G, Frasese GV, De Maria R, *et al*: The inhibition of the highly expressed miR-221 and miR-222 impairs the growth of prostate carcinoma xenografts in mice. *PLoS One* 3: e4029, 2008.
316. Zhao Y, Zhao L, Ischenko I, Bao Q, Schwarz B, Nieß H, Wang Y, Renner A, Mysliwicz J, Jauch KW, *et al*: Antisense inhibition of microRNA-21 and microRNA-221 in tumor-initiating stem-like cells modulates tumorigenesis, metastasis, and chemotherapy resistance in pancreatic cancer. *Target Oncol* 10: 535-548, 2015.
317. Wagenaar TR, Zabudoff S, Ahn SM, Allerson C, Arlt H, Baffa R, Cao H, Davis S, Garcia-Echeverria C, Gaur R, *et al*: Anti-miR-21 suppresses hepatocellular carcinoma growth via broad transcriptional network deregulation. *Mol Cancer Res* 13: 1009-1021, 2015.
318. Fabani MM, Abreu-Goodger C, Williams D, Lyons PA, Torres AG, Smith KG, Enright AJ, Gait MJ and Vígortó E: Efficient inhibition of miR-155 function in vivo by peptide nucleic acids. *Nucleic Acids Res* 38: 4466-4475, 2010.
319. Brognara E, Fabbri E, Aimi F, Manicardi A, Bianchi N, Finotti A, Breveglieri G, Borgatti M, Corradini R, Marchelli R, *et al*: Peptide nucleic acids targeting miR-221 modulate p27^{Kip1} expression in breast cancer MDA-MB-231 cells. *Int J Oncol* 41: 2119-2127, 2012.

320. Yan LX, Wu QN, Zhang Y, Li YY, Liao DZ, Hou JH, Fu J, Zeng MS, Yun JP, Wu QL, *et al*: Knockdown of miR-21 in human breast cancer cell lines inhibits proliferation, *in vitro* migration and *in vivo* tumor growth. *Breast Cancer Res* 13: R2, 2011.
321. Zhang J and Ma L: MicroRNA control of epithelial-mesenchymal transition and metastasis. *Cancer Metastasis Rev* 31: 653-662, 2012.
322. Zaravinos A, Radojicic J, Lambrou GI, Volanis D, Delakas D, Stathopoulos EN and Spandidos DA: Expression of miRNAs involved in angiogenesis, tumor cell proliferation, tumor suppressor inhibition, epithelial-mesenchymal transition and activation of metastasis in bladder cancer. *J Urol* 188: 615-623, 2012.
323. Kiesslich T, Pichler M and Neureiter D: Epigenetic control of epithelial-mesenchymal-transition in human cancer. *Mol Clin Oncol* 1: 3-11, 2013.
324. Lei C, Wang Y, Huang Y, Yu H, Huang Y, Wu L and Huang L: Up-regulated miR155 reverses the epithelial-mesenchymal transition induced by EGF and increases chemo-sensitivity to cisplatin in human Caski cervical cancer cells. *PLoS One* 7: e52310, 2012.
325. Koutsaki M, Spandidos DA and Zaravinos A: Epithelial-mesenchymal transition-associated miRNAs in ovarian carcinoma, with highlight on the miR-200 family: Prognostic value and prospective role in ovarian cancer therapeutics. *Cancer Lett* 351: 173-181, 2014.
326. Gao H, Teng C, Huang W, Peng J and Wang C: SOX2 promotes the epithelial to mesenchymal transition of esophageal squamous cells by modulating Slug expression through the activation of STAT3/HIF- α signaling.
327. Lambertini E, Lolli A, Vezzali F, Penolazzi L, Gambari R and Piva R: Correlation between Slug transcription factor and miR-221 in MDA-MB-231 breast cancer cells. *BMC Cancer* 12: 445, 2012.
328. Qiu G, Lin Y, Zhang H and Wu D: miR-139-5p inhibits epithelial-mesenchymal transition, migration and invasion of hepatocellular carcinoma cells by targeting ZEB1 and ZEB2. *Biochem Biophys Res Commun* 463: 315-321, 2015.
329. Bezzerra V, Borgatti M, Finotti A, Tamanini A, Gambari R and Cabrini G: Mapping the transcriptional machinery of the IL-8 gene in human bronchial epithelial cells. *J Immunol* 187: 6069-6081, 2011.
330. Raychaudhuri B and Vogelbaum MA: IL-8 is a mediator of NF- κ B induced invasion by gliomas. *J Neurooncol* 101: 227-235, 2011.
331. Xie TX, Xia Z, Zhang N, Gong W and Huang S: Constitutive NF- κ B activity regulates the expression of VEGF and IL-8 and tumor angiogenesis of human glioblastoma. *Oncol Rep* 23: 725-732, 2010.
332. Sun S, Wang Q, Giang A, Cheng C, Soo C, Wang CY, Liau LM and Chiu R: Knockdown of CypA inhibits interleukin-8 (IL-8) and IL-8-mediated proliferation and tumor growth of glioblastoma cells through down-regulated NF- κ B. *J Neurooncol* 101: 1-14, 2011.
333. Gabellini C, Castellini L, Trisciuglio D, Kracht M, Zupi G and Del Bufalo D: Involvement of nuclear factor-kappa B in bcl-xL-induced interleukin 8 expression in glioblastoma. *J Neurochem* 107: 871-882, 2008.
334. Yang TQ, Lu XJ, Wu TF, Ding DD, Zhao ZH, Chen GL, Xie XS, Li B, Wei YX, Guo LC, *et al*: MicroRNA-16 inhibits glioma cell growth and invasion through suppression of BCL2 and the nuclear factor- κ B1/MMP9 signaling pathway. *Cancer Sci* 105: 265-271, 2014.
335. Fang L, Deng Z, Shatseva T, Yang J, Peng C, Du WW, Yee AJ, Ang LC, He C, Shan SW, *et al*: MicroRNA miR-93 promotes tumor growth and angiogenesis by targeting integrin- β 8. *Oncogene* 30: 806-821, 2011.
336. Magge SN, Malik SZ, Royo NC, Chen HI, Yu L, Snyder EY, O'Rourke DM and Watson DJ: Role of monocyte chemoattractant protein-1 (MCP-1/CCL2) in migration of neural progenitor cells toward glial tumors. *J Neurosci Res* 87: 1547-1555, 2009.
337. Nazarenko I, Hede SM, He X, Hedrn A, Thompson J, Lindström MS and Nistér M: PDGF and PDGF receptors in glioma. *Ups J Med Sci* 117: 99-112, 2012.
338. Cai JJ, Qi ZX, Chen LC, Yao Y and Gong Y and Mao Y: miR-124 suppresses the migration and invasion of glioma cells *in vitro* via Capn4. *Oncol Rep* 35: 284-290, 2015.
339. Cheng Y, Li Y, Nian Y, Liu D, Dai F and Zhang J: STAT3 is involved in miR-124-mediated suppressive effects on esophageal cancer cells. *BMC Cancer* 15: 306, 2015.
340. Dong LL, Chen LM, Wang WM, Zhang LM: Decreased expression of microRNA-124 is an independent unfavorable prognostic factor for patients with breast cancer. *Diagn Pathol* 10: 45, 2015.
341. Long QZ, Du YF, Liu XG, Li X and He DL: miR-124 represses FZD5 to attenuate P-glycoprotein-mediated chemo-resistance in renal cell carcinoma. *Tumour Biol* 36: 7017-7026, 2015.
342. Lu SH, Jiang XJ, Xiao GL, Liu DY and Yuan XR: miR-124a restoration inhibits glioma cell proliferation and invasion by suppressing IQGAP1 and β -catenin. *Oncol Rep* 32: 2104-2110, 2014.
343. Chen SM, Chou WC, Hu LY, Hsiung CN, Chu HW, Huang YL, Hsu HM, Yu JC and Shen CY: The Effect of MicroRNA-124 overexpression on anti-tumor drug sensitivity. *PLoS One* 10: e0128472, 2015.
344. Fabbri E, Brognara E, Montagner G, Ghimenton C, Eccher A, Cantù C, Khalil S, Bezzerra V, Provezza L, Bianchi N, *et al*: Regulation of IL-8 gene expression in gliomas by microRNA miR-93. *BMC Cancer* 15: 661, 2015.
345. Fabbri E, Montagner G, Bianchi N, Finotti A, Borgatti M, Lampronti I, Cabrini G and Gambari R: MicroRNA miR-93-5p overregulates expression of IL-8 and VEGF in neuroblastoma SK-N-AS cells. *Oncol Rep* 35: 2866-2872, 2016.
346. Galardi S, Mercatelli N, Giorda E, Massalini S, Frajese GV, Ciafrè SA and Farace MG: miR-221 and miR-222 expression affects the proliferation potential of human prostate carcinoma cell lines by targeting p27^{Kip1}. *J Biol Chem* 282: 23716-23724, 2007.
347. Lu X, Zhao P, Zhang C, Fu Z, Chen Y, Lu A, Liu N, You Y, Pu P and Kang C: Analysis of miR-221 and p27 expression in human gliomas. *Mol Med Rep* 2: 651-656, 2009.
348. Gillies JK and Lorimer IA: Regulation of p27^{Kip1} by miRNA 221/222 in glioblastoma. *Cell Cycle* 6: 2005-2009, 2007.
349. Wang Y, Wang X, Zhang J, Sun G, Luo H, Kang C, Pu P, Jiang T, Liu N and You Y: MicroRNAs involved in the EGFR/PTEN/AKT pathway in gliomas. *J Neurooncol* 106: 217-224, 2012.
350. Ueda R, Kohanbash G, Sasaki K, Fujita M, Zhu X, Kastenhuber ER, McDonald HA, Potter DM, Hamilton RL, Lotze MT, *et al*: Dicer-regulated microRNAs 222 and 339 promote resistance of cancer cells to cytotoxic T-lymphocytes by down-regulation of ICAM-1. *Proc Natl Acad Sci USA* 106: 10746-10751, 2009.
351. Zhang J, Han L, Ge Y, Zhou X, Zhang A, Zhang C, Zhong Y, You Y, Pu P and Kang C: miR-221/222 promote malignant progression of glioma through activation of the Akt pathway. *Int J Oncol* 36: 913-920, 2010.
352. Zhang C, Jiang T, Wang J, Cheng J, Pu P and Kang C: MiR-221/222 promote the growth of malignant glioma cells by regulating its target genes, molecular targets of CNS tumors. Dr Miklos Garami (Ed). ISBN: 978-953-307-736-9. InTech, pp461-482, 2011.
353. Sarkar S, Dubaybo H, Ali S, Goncalves P, Kollepara SL, Sethi S, Philip PA and Li Y: Down-regulation of miR-221 inhibits proliferation of pancreatic cancer cells through up-regulation of PTEN, p27(kip1), p57(kip2), and PUMA. *Am J Cancer Res* 3: 465-477, 2013.
354. Zhang C, Kang C, You Y, Pu P, Yang W, Zhao P, Wang G, Zhang A, Jia Z, Han L, *et al*: Co-suppression of miR-221/222 cluster suppresses human glioma cell growth by targeting p27^{Kip1} *in vitro* and *in vivo*. *Int J Oncol* 34: 1653-1660, 2009.
355. Zhang R, Pang B, Xin T, Guo H, Xing Y, Xu S, Feng B, Liu B and Pang Q: Plasma miR-221/222 family as novel descriptive and prognostic biomarkers for glioma. *Mol Neurobiol* 53: 1452-1460, 2016.
356. Yang Y, Li F, Saha MN, Abdi J, Qiu L and Chang H: miR-137/197 induce apoptosis and suppress tumorigenicity by targeting MCL-1 in multiple myeloma. *Clin Cancer Res* 21: 2399-2411, 2015.
357. Lee SH, Jung YD, Choi YS and Lee YM: Targeting of RUNX3 by miR-130a and miR-495 cooperatively increases cell proliferation and tumor angiogenesis in gastric cancer cells. *Oncotarget* 6: 33269-33278, 2015.
358. Brognara E, Fabbri E, Montagner G, Gasparello J, Manicardi A, Corradini R, Bianchi N, Finotti A, Breveglieri G, Borgatti M, *et al*: High levels of apoptosis are induced in human glioma cell lines by co-administration of peptide nucleic acids targeting miR-221 and miR-222. *Int J Oncol* 48: 1029-1038, 2016.
359. Giunti L, da Ros M, Vinci S, Gelmini S, Iorio AL, Buccoliero AM, Cardellicchio S, Castiglione F, Genitori L, de Martino M, *et al*: Anti-miR21 oligonucleotide enhances chemosensitivity of T98G cell line to doxorubicin by inducing apoptosis. *Am J Cancer Res* 5: 231-242, 2014.

360. Gao C, Peng FH and Peng LK: MiR-200c sensitizes clear-cell renal cell carcinoma cells to sorafenib and imatinib by targeting heme oxygenase-1. *Neoplasma* 61: 680-689, 2014.
361. Pogribny IP, Filkowski JN, Tryndyak VP, Golubov A, Shpyleva SI and Kovalchuk O: Alterations of microRNAs and their targets are associated with acquired resistance of MCF-7 breast cancer cells to cisplatin. *Int J Cancer* 127: 1785-1794, 2010.
362. Suto T, Yokobori T, Yajima R, Morita H, Fujii T, Yamaguchi S, Altan B, Tsutsumi S, Asao T and Kuwano H: MicroRNA-7 expression in colorectal cancer is associated with poor prognosis and regulates cetuximab sensitivity via EGFR regulation. *Carcinogenesis* 36: 338-345, 2015.
363. Liu R, Liu X, Zheng Y, Gu J, Xiong S, Jiang P, Jiang X, Huang E, Yang Y, Ge D, *et al*: MicroRNA-7 sensitizes non-small cell lung cancer cells to paclitaxel. *Oncol Lett* 8: 2193-2200, 2014.
364. Gomes SE, Simões AE, Pereira DM, Castro RE, Rodrigues CM and Borralho PM: miR-143 or miR-145 overexpression increases cetuximab-mediated antibody-dependent cellular cytotoxicity in human colon cancer cells. *Oncotarget*: Jan 25, 2016 (Epub ahead of print).
365. Costa PM, Cardoso AL, Nóbrega C, Pereira de Almeida LF, Bruce JN, Canoll P and Pedrosa de Lima MC: MicroRNA-21 silencing enhances the cytotoxic effect of the antiangiogenic drug sunitinib in glioblastoma. *Hum Mol Genet* 22: 904-918, 2013.
366. Qian X, Ren Y, Shi Z, Long L, Pu P, Sheng J, Yuan X and Kang C: Sequence-dependent synergistic inhibition of human glioma cell lines by combined temozolomide and miR-21 inhibitor gene therapy. *Mol Pharm* 9: 2636-2645, 2012.
367. Zhang S, Han L, Wei J, Shi Z, Pu P, Zhang J, Yuan X and Kang C: Combination treatment with doxorubicin and microRNA-21 inhibitor synergistically augments anticancer activity through upregulation of tumor suppressing genes. *Int J Oncol* 46: 1589-1600, 2015.
368. Zhang Q, Ran R, Zhang L, Liu Y, Mei L, Zhang Z, Gao H and He Q: Simultaneous delivery of therapeutic antagomirs with paclitaxel for the management of metastatic tumors by a pH-responsive anti-microbial peptide-mediated liposomal delivery system. *J Control Release* 197: 208-218, 2015.
369. Fan L, Yang Q, Tan J, Qiao Y, Wang Q, He J, Wu H and Zhang Y: Dual loading miR-218 mimics and Temozolomide using AuCOOH[®]FA-CS drug delivery system: Promising targeted anti-tumor drug delivery system with sequential release functions. *J Exp Clin Cancer Res* 34: 106, 2015.
370. Xue W, Dahlman JE, Tammela T, Khan OF, Sood S, Dave A, Cai W, Chirino LM, Yang GR, Bronson R, *et al*: Small RNA combination therapy for lung cancer. *Proc Natl Acad Sci USA* 111: E3553-E3561, 2014.
371. Nishimura M, Jung EJ, Shah MY, Lu C, Spizzo R, Shimizu M, Han HD, Ivan C, Rossi S, Zhang X, *et al*: Therapeutic synergy between microRNA and siRNA in ovarian cancer treatment. *Cancer Discov* 3: 1302-1315, 2013.
372. Hu X, Li W, Liu G, Wu H, Gao Y, Chen S, He D and Zhang Y: The effect of Bcl-2 siRNA combined with miR-15a oligonucleotides on the growth of Raji cells. *Med Oncol* 30: 430, 2013.