Function of miRNAs in Tumor Cell Proliferation

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Abstract MicroRNAs (miR) are a class of multifunctional, small, non-coding, singled-stranded molecules that regulate the stability or translational efficiency of targeted messenger RNAs. According to the miRBase Sequence Database (http://www.mirbase.org/index.shtml), more than 1,000 miR sequences have been identified from the tissues or cells of human origin. miRNAs are transcribed from the genome mostly by RNA polymerase II into primary miRNAs (called pri-miRNA) which are usually around 1 kb in length. pri-miRNAs are further processed in the nucleus by a ribonucleases complex composed of Drosha and DGCR8 into precursor miRNAs (called pre-miRNAs) which are around 70–90 nucleotides in length with imperfectly complementary stem-loop-stem structures. The pre-miRNA is then transported by exportin-5, a pre-miRNA-specific export carrier, to the cytoplasm where the pre-miRNA is cleaved by another ribonuclease, Dicer, into a double-stranded miRNA which consists of a mature miRNA sequence of about 17–25 nucleotides long and a miRNA* fragment (derived from the opposite strand to the mature miRNA strand). The mature miRNA is assembled into a ribonucleoprotein complex known as RNA-induced silencing complex (RISC) that includes Argonaute protein [1]. The miR-RISC complex could lead to base-pairing interactions between a miRNA and the binding site of its target mRNAs within the 3' untranslated region (3'UTR). The interaction could lead to endonucleotic cleavage of the target mRNA or interference with its ability to be translated depending on the base-pairing complementarity between the miRNA and the target mRNA [2, 3].

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1 Introduction

MicroRNAs (miR) are a class of multifunctional, small, non-coding, singled-stranded molecules that regulate the stability or translational efficiency of targeted messenger RNAs. According to the miRBase Sequence Database (http://www.mirbase.org/index.shtml), more than 1,000 miR sequences have been identified from the tissues or cells of human origin. miRNAs are transcribed from the genome mostly by RNA polymerase II into primary miRNAs (called pri-miRNA) which are usually around 1 kb in length. pri-miRNAs are further processed in the nucleus by a ribonucleases complex composed of Drosha and DGCR8 into precursor miRNAs (called pre-miRNAs) which are around 70–90 nucleotides in length with imperfectly complementary stem-loop-stem structures. The pre-miRNA is then transported by exportin-5, a pre-miRNA-specific export carrier, to the cytoplasm where the pre-miRNA is cleaved by another ribonuclease, Dicer, into a double-stranded miRNA which consists of a mature miRNA sequence of about 17–25 nucleotides long and a miRNA* fragment (derived from the opposite strand to the mature miRNA strand). The mature miRNA is assembled into a ribonucleoprotein complex known as RNA-induced silencing complex (RISC) that includes Argonaute protein [1]. The miR-RISC complex could lead to base-pairing interactions between a miRNA and the binding site of its target mRNAs within the 3′ untranslated region (3′UTR). The interaction could lead to endonucleotic cleavage of the target mRNA or interference with its ability to be translated depending on the base-pairing complementarity between the miRNA and the target mRNA [2, 3].

The target identification of miRNAs remains challenging due to the lack of a confident criteria or effective ways to predict targets accurately. Nevertheless, different bioinformatics approaches have been applied to search the putative targets for a particular miRNA. Usually the nucleotides 2–8 (called “seed” sequence) of a miRNA are considered as the most important sequence for binding to target mRNA. A perfect complementarity between target mRNA 3’UTR to the “seed” sequence of a miRNA is required for the target prediction. At this point each vertebrate miRNA is supposed to bind to as many as hundreds gene targets or even more. And each gene may contain multiple binding sites for different miRNAs. miRNAs have the potential to target about one-third of human mRNAs [4]. However, the regulatory interaction between any predicted target gene and a particular miRNA has to be experimentally confirmed, usually through luciferase reporter assays.

miRNAs have been demonstrated to regulate a broad range of biological processes including timing of development, cell cycle progression, embryonic stem cell, cancer stem cell, cancer initiation, cancer cell proliferation, cancer metastasis and apoptosis [5–11]. Cancer is caused by multiple processes including uncontrolled proliferation and the inappropriate survival of damaged cells. Many regulatory factors switch on or off genes that direct cellular proliferation and differentiation. Emerging evidence indicates miRNAs are involved in tumorigenesis and function as tumor suppressors or oncogenes [9]. Altered expression of miRNAs or mutations of miRNA genes have been described in different types of human cancer.

For example, let-7 is downregulated in several cancers including lung cancer [12]; miR-15a and miR16-1 are deleted and/or down-regulated in ~70 % of patients with chronic lymphocytic leukemia [13]; miR-17/20a are decreased in abundance in tumor sample from breast cancer patient compared to the matching sample from same patient [14]. The expression level of a particular miRNA varies by cell type. Thus the same miRNA may perform different functions through distinct pathways dependent on the tissue or cell type. It is important to understand the tumor cell type-specific pathway through which a miRNA regulates cancer cell proliferation and tumorigenesis.

2 Aberrant miRNA Expression in Cancer

miRNAs were linked to cancer very soon after their discovery. The first report linking miRNA to cancer patient was in 2002 by Calin et al. showing that miR-15 and miR-16 are located at chromosome 13q14, a region deleted in more than half of B cell chronic lymphocytic leukemias (B-CLL) [13]. Both of the miRNAs are deleted or down-regulated in approximately 68 % of CLL patients. Their further study mapping 186 miRNA locations in the genome indicated that 52.5 % of miRNA genes are located at cancer-associated genomic regions or in fragile sites [8]. In 2005, Lorio et al. identified 29 miRNAs with aberrant expression in human breast cancer by microarray and northern blot analyses on 76 breast tumor samples and 14 human breast cell lines [15]. Jiang et al. detected 222 human miRNA precursors in expression profile of 32 human cell lines from lung, breast, colorectal, hematologic, prostate, pancreatic, and head and neck cancers [16]. Several miRNAs had tissue-specific aberrant expression including miR-205 which showed 36-fold higher abundance in head and neck cancer cell lines than other cell lines. In 2006, Zhang and colleagues performed an analysis of 283 known human miRNA genes by array-based comparative genomic hybridization in 227 human ovarian cancer, breast cancer, and melanoma specimens demonstrating the high-frequency gene copy number abnormality of miRNA-containing regions throughout the genome in human ovarian cancer (37.1 %), breast cancer (72.8 %), and melanoma (85.9 %) [17]. Murakami et al. analyzed the miRNA expression profiles in 25 pairs of hepatocellular carcinoma (HCC), adjacent non-tumorous tissue (NT) and nine additional chronic hepatitis (CH) specimens using a human miRNA microarray [18]. Three miRNAs (miR-224, miR-18 and pre-miR-p18) exhibited higher expression and five miRNAs (miR-199a, miR-199a*, miR-200a, miR-125a and miR-195) showed lower expression in the HCC samples compared to the NT samples. Yanaihara et al. analyzed the miRNA expression in 104 pairs of primary lung cancers and corresponding non-cancerous lung tissues, and identified 43 miRNAs with differential expression in lung cancer [19]. Many of these miRNAs are located at frequently deleted or amplified regions in several malignancies. For example, miR-21 and miR-205 are located at the region amplified in lung cancer, whereas hsa-mir-126* and hsa-mir-126 are at a region deleted in lung cancer. Reduced expression of precursor let-7a and let-7f

was also found in adenocarcinoma and squamous cell carcinoma. In 2007, Porkka et al. examined the miRNA expression profiling of six prostate cancer cell lines, nine prostate cancer xenografts samples, four benign prostatic hyperplasia, and nine prostate carcinoma samples using an oligonucleotide microarray [20]. They identified 51 miRNAs aberrantly expressed in prostate cancer including 37 miRNAs down-regulated and 14 miRNAs up-regulated in the prostate carcinoma samples. Gottardo et al. reported four human miRNAs (miR-28, miR-185, miR-27, and let-7f-2) significantly up-regulated in renal cell carcinoma compared to normal kidney, and ten human miRNAs (miR-223, miR-26b, miR-221, miR-103-1, miR-185, miR-23b, miR-203, miR-17–5p, miR-23a, and miR-205) up-regulated in bladder cancers compared to normal bladder mucosa [21]. In 2008, Schepeler et al. profiled the expression of 315 human miRNAs in ten normal mucosa samples and 49 stage II colon cancers using microarray technology [22]. Comparing with normal mucosa, 25 miRNAs were differentially expressed (7 down; 18 up) in microsatellite unstable colon cancers, and 54 miRNAs were differentially expressed (29 down; 25 up) in microsatellite stable colon cancers. miR-145 was identified as the lowest expression in colon cancer relative to normal tissue.

These studies provide evidence for new mechanisms by which aberrant expression of miRNAs and/or the loss or the gain of miRNA-containing genomic regions in a specific type of cancer may contribute to tumorigenesis. miRNAs may therefore serve as new diagnostic biomarkers and/or therapeutic tools for human cancers.

3 miRNA Regulation of Tumor Cell Division

Cancer is characterized by loss of cellular growth control, excess of cellular proliferation and altered cellular metabolism, invasion and metastasis. Understanding the mechanisms controlling cell division is important to developing novel anti-cancer therapies. Cyclins and cyclin-dependent kinases (CDKs) determine cell cycle progression. The mechanisms by which miRNAs regulate the cell cycle are increasingly well understood. Controlling cell-cycle represents new approaches to tumor cell inhibition.

3.1 Cell Division Cycle

Cyclin D1 serves as a cell cycle regulatory switch in actively proliferating cells. The *cyclin D1* gene encodes the regulatory subunit of the holoenzyme that phosphorylates and inactivates the pRb protein to promote G_1/S transition. Cyclin D1 binds to CDK4/6 forming the active complex, phosphorylates the retinoblastoma (Rb) resulting in the Rb dissociation from E2F complexes resulting in the transcriptional regulation of genes which contain E2F sites in their promoters such as cyclin E, cyclin A, DNA polymerase, thymidine kinase. Cyclin E binds to CDK2 forming the

cyclin E-CDK2 complex, which pushes the cell cycle G_1/S transition. The cyclin A-CDK2 complex activates DNA synthesis. The cyclin B-cdc2 complex initiates the G_2/M transition. In contrary to the positive regulation of cell division cycle by cyclins and CDKs, two inhibitory families encode negative regulators of the cell cycle. The *cip/kip* family includes $p21^{CIP1}$, $p27^{KIP1}$and $p57^{KIP2}$ which arrest cell cycle at G_1 phase by inactivating cyclin-CDK complexes, and INK4a/ARF family including $p16^{INK4a}$ and $p14^{arf}$ [23].

Cyclin D1 is overexpressed in several cancer types including breast, esophageal and thyroid cancer, encoding a rate-limiting factor for proliferation of cancer cells in tissue culture [24–26]. Inhibition of *cyclin D1* expression *in vivo* suppressed breast cancer cell proliferation in nude nice [28]. Cyclin E is ovexpressed in 10 % of breast cancers. Emerging evidences have shown that miRNAs interact with *cyclins*, cyclin-dependent kinases (CDKs), *E2F*, *Rb* and CDK inhibitors thereby regulating cellular division and tumor growth [14, 27–30].

3.2 miRNAs Inhibiting Tumor Cell Proliferation

3.2.1 miR-15a and miR-16-1

miR-15a and miR-16-1 are deleted and/or down-regulated in chronic lymphocytic leukemia patients [13], prostate cancer [31] and pituitary tumors [32]. The anti-apoptotic gene BCL2 is negatively regulated by miR-15a and miR-16-1, leading to the inhibition of tumor growth. miR-15a and miR-16-1 induce cell cycle arrest at the G_1 phase by targeting cell cycle regulators including cyclin D1, cyclin E1, cyclin D3 and CDK6 [33, 34].

3.2.2 miR-17/20

miR-17/20 expression is decreased in human breast cancer specimen compared to the matching normal tissue suggesting a tumor suppressor function in breast cancer [14]. miR-17/20 binds to the cyclin D1 3'UTR in the MCF-7 breast cancer cells, inhibits the expression of cyclin D1, resulting in cell cycle arrest and suppression of cell proliferation [14, 35]. Besides cyclin D1, other cell-cycle related genes are regulated by miR-17/20 thereby controlling cell cycle progression [35].

3.2.3 miR-221/222

miR-221/222 is a miRNA cluster targeting the CDK inhibitors $p27^{KIP1}$ and $p57^{KIP2}$ [36]. miR-221/222 cluster ectopic expression decreases $p27^{KIP1}$ and $p57^{KIP2}$ abundance, activating cyclin E-CDK2 and cyclin A-CDK2 complexes, facilitating the G_1/S phase transition and DNA synthesis. This has been demonstrated in both human breast cancer and gastric cancer [30, 36].

3.2.4 Let-7

Let-7 is a tumor suppressor miRNA family. Let-7 family members are down-regulated in lung [12], colon [37], ovarian [38] and breast cancer [39]. Let-7 regulates tumorigenesis via *Ras*, *HMGA2, MYC* and/or *caspase-3* [39–43]. Let-7 overexpression inhibits tumor cell proliferation by targeting cyclin D1, cyclin D3, cyclin A, CDK 4 [44] and *CCNA2, CDC25 A,CDK6* and *CDK8* [45].

3.2.5 miR-29

miR-29 family (miR-29a, 29b, and 29c) have been associated with acute myelogeneous leukemia (AML), rhabdomyosarcoma, hepatocellular carcinoma and mantle cell lymphoma [46–49] by regulating cell apoptosis, cell cycle, and cell proliferation pathways. miR-29 overexpression induces apoptosis and inhibits tumor cell proliferation *in vitro*. In mantle cell lymphoma miR-29 inhibits CDK6 protein and mRNA levels. The down-regulation of miR-29 may cooperate with cyclin D1 in MCL pathogenesis [49].

3.2.6 miR-34, miR-192 and miR-215

miR-34, miR-192 and miR-215 regulate the p53 tumor suppressor network [50]. miR-34 overexpression arrests the cell cycle, induces apoptosis and inhibits cancer cell proliferation and colony formation by downregulating cyclin D1, cyclin E2, E2Fs and CDK4/6 [50–53]. miR-192 and miR-215 expression is reduced in colon cancer samples, and miR-192/ miR-215 suppresses colony formation and carcinogenesis via $p21^{CIP1}$ accumulation and cell cycle arrest [54]. $p21^{CIP1}$ accumulation is partially dependent on the presence of wild-type p53.

3.3 miRNAs Enhancing Tumor Cell Proliferation

3.3.1 miR-21

miR-21 overexpression has been observed frequently in a wide variety of cancers including breast cancer [55, 56], lung cancer [19] and liver cancer [57]. miR-21 induces MCF-7 cell-derived breast tumor growth in the xenograft mouse model [55]. In MCF-7 cells, miR-21 targets the antiapoptotic gene Bcl-2 [55], the tumor-suppressor gene *tropomyosin 1* (*TPM1*) [58] and the tumor suppressor protein Programmed Cell Death 4 (PDCD4) [56]. In human hepatocellular cancer cells miR-21 targets the tumorsuppressor gene PTEN, thereby enhancing tumor cell proliferation, migration, and invasion [57].

3.3.2 miR-27a

miR-27a expression is upregulated in kidney cancers [21] and breast cancer cell lines [59]. The zincfinger *ZBTB10* gene is a direct target of miR-27a [59]. InMDA-MB-231 human breast cancer cells, miR-27a inactivation induced *ZBTB10* expressionand reduced expression of oncogene *specificity proteins* (*Sp1*, *Sp3*, and *Sp4*) at the mRNA and protein levels [60]. The cyclin B-cdc2 complex inhibitor *Myt-1* is another target of miR-27a [60]. In MDA-MB-231cells miR-27a inhibits *Myt-1* expression increasing Cyclin B-cdc2 activity thereby promoting breast cancer cell proliferation.

3.3.3 miR-155

miR-155 is frequently up-regulated in breast cancer [61], lung cancer [19], pancreatic [62] and lymphomas [63]. In breast cancer, miR-155 expression induces cell survival, growth and chemoresistance by targeting the FOXO3a gene [61]. In pancreatic ductal adenocarcinoma (PDAC) cells, miR-155 is oncogenic by targeting the tumor suppressor gene *tumor protein 53-induced nuclear protein 1* (TP53INP1) [62].

4 miRNA Regulation of Cancer Stem Cells

Cancer stem cells (CSCs) are a subpopulation of stem-like cells within tumors. CSCs are characterized by their self-renewal capacity, an ability to differentiate into non-tumorigenic cell progeny, and their ability to seed tumors when transplanted into animal hosts [65]. CSCs have been demonstrated in several solid tumors including human breast cancer and brain cancer [64, 66], and melanoma, glioblastoma colon, pancreas, lung and prostate cancers. CSCs are isolated and enriched on the basis of cell surface markers (CD44, CD24 and/or CD133) dependent on tumor type. The leukaemic stem-like cells are fractioned by $CD34^{++}$ $CD38^{-}$ [67]; the mammary tumorigenic CSCs are isolated by $CD44^{+}$ $CD^{24-/low}lineage^{-}$ [65]; the colon CSCs are isolated by $CD133^{+}$ [68]. Recently epithelial-specific antigen (ESA) and aldehyde dehydrogenase-1 (ALDH-1) were added into the candidate list of CSC-specific markers [69, 70, 71].

miRNAs regulate self-renewal and differentiation of ES cells, adult tissue stem cells, and CSCs. A subset of miRNAs (miR-142-3p, miR-451, miR-106a, miR-142-5p, miR-15b, miR-20a, miR-106b, miR-25 and miR-486) has altered expression in lung cancer progenitor cells [72]. Thirty seven miRNAs were deregulated in human breast cancer stem cells ($CD44^{+}$ $CD24^{-/low}lineage^{-}$) compared to the lineage- nontumorigenic breast cancer cells [73]. Notably, members of miR-200 family including miR-200a, miR-200b and miR-200c, were down-regulated in the breast cancer stem cell population. The miR-200 family regulates epithelial to mesenchymal transition (EMT) in breast cancer [74]. Let-7 has a low expression in breast CSCs and

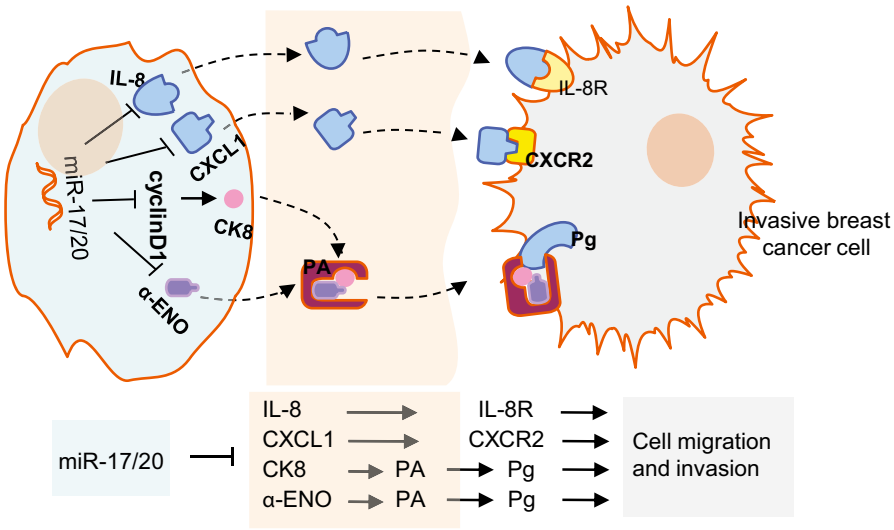

Fig. 1 miR-17/20 regulates cancer cell migration and invasion via heterotypic secreted signals *Pg* plasminogen, *PA* plasminogen activator, *IL-8R* IL-8 receptor, *CXCR2 CXCL1* receptor

increases with differentiation. Let-7 regulates self renewal and tumorigenicity of breast cancer stem cells [39]. Expression of let-7 in breast CSCs reduced proliferation, mammosphere formation, and the proportion of undifferentiated cells *in vitro* and tumor formation and metastasis in NOD/SCID mice [39].

5 miRNA Regulation of Tumor Microenvironment and Cancer Metastasis

The regulation of the tumor microenvironment to promote tumorigenesis was proposed by Paget in his 'soil and seed' hypothesis of cancer metastasis. Carcinogenesis and metastasis are controlled by both internal and external "heterotypic" signals from the surrounding cells and environment. Cancer metastases represent a complex process by which primary solid tumor cells invade adjacent tissue and grow into secondary tumors. miR-373 and miR-520c stimulate breast cancer cell migration and invasion by suppressing the gene *CD44* [75]; miRNA-200 and miR 205 inhibit EMT in breast cancer [74]. Our recent studies demonstrated a novel mechanism by which miRNA regulates cancer cell migration and invasion via heterotypic secreted signals (Fig. 1) [76]. miR-17/20 conditioned medium from cultures of MCF7 cells (a non-metastatic line) inhibited the migration and invasion of MDA-MB-231 cells (a metastatic line). miR-17/20 decreased the abundance of secreted factors such as cytokines (IL-8, CXCL1) and plasminogen activators (cytokeratin 8/18 and α-enolase) in MCF-7 cells. These secreted factors were essential for migration of the cancer cells. As miRNAs and the cancer microenvironment have a

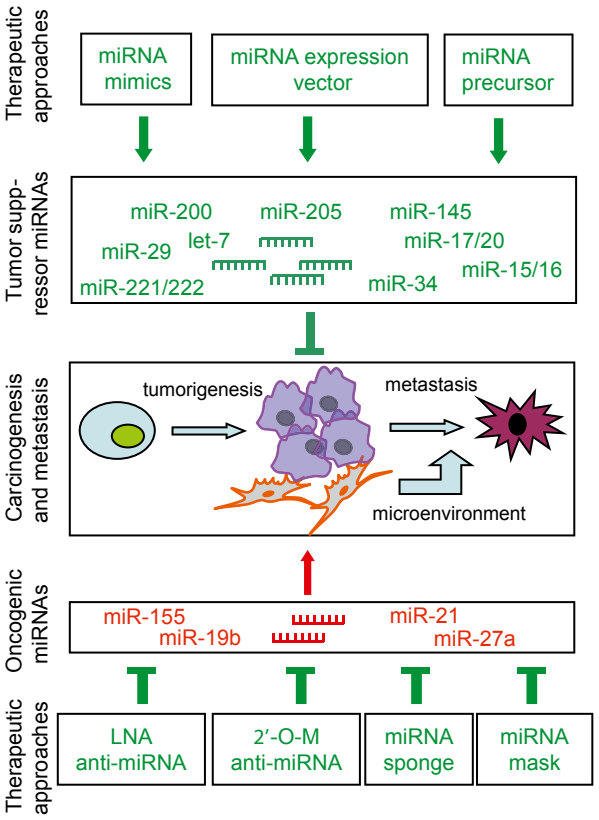

Fig. 2 miRNA-based cancer diagnostic and therapeutic strategies

crucial role in tumorigenesis and metastasis, these studies identify a potential new site of invention via inhibition of miRNA-regulated secreted factors.

6 Therapeutic Application of miRNA in Cancer

MiRNA-based cancer diagnostic and therapeutic approaches are being established and tested in animal models. There are two strategies for miRNA-based therapeutic application in cancers: expression-based restoration of tumor suppressor miRNA and functional inhibition of oncogenic miRNA (Fig. 2).

6.1 Restoring the Expression of Tumor Suppressor miRNAs

Two lines of evidence suggest miRNAs function as tumor suppressor rather than oncogenes. The global decrease of miRNA expression in cancer tissues compared

to normal control [77], and the enhanced cellular transformation and tumorigenesis by impaired miRNA processing [78]. Synthetic miRNA mimics or miRNA expression vectors carrying either a pre-miRNA sequence or an artificial miRNA hairpin sequence have been widely used to perform the miRNA expression restoring *in vitro*. Recent publications demonstrated that miRNA reintroduction suppresses tumor growth *in vivo* [79, 80, 81]. Intranasal delivery of exogenous let-7 mimics to the lung tumors of mice (non-small-cell lung cancer) reduced the tumor burden [80]. Intravenous delivery of miR-34a mimics using a lipid-based delivery vehicle accumulated miR-34a in the tumor tissue in mouse models of non-small-cell lung cancer, and blocked tumor growth. Furthermore, this approach did not induce an immune response [81]. An adeno-associated virus (AAV)-mediated delivery of *miR-26a* to mouse liver resulted in reduced liver cancer cell proliferation, induction of tumor-specific apoptosis, and protection from disease progression without toxicity [82].

6.2 Blocking the Function of Oncogenic miRNAs

Since a small number of miRNAs show oncogenic function, such as miR-21, decreasing the expression level or blocking the function of those oncogenic miRNAs is another strategy for cancer therapy. Chemically modified antisense oligonucleotides (called anti-miRNA) are used most frequently to knock down miRNA *in vitro*. The modification includes addition of 2′-O-methyl, addition of 2′-O-methoxyethyl and locked nucleic acid (LNA) with 2′-O connecting to 4′-C. The modified nucleic acid structure has high affinity and high specificity to bind with target miRNA. Moreover, the anti-miRNA–miRNA structure is highly stable. As such the delivery of a specific anti-miRNA into cells prevents the miRNA from binding to their cognate target genes thereby silencing miRNA function.

Recently two more approaches were reported for blocking miRNAs. One is called the miRNA-sponge [83] which serves as a competitive inhibitor of miRNAs. An expression vector carrying multiple binding sites to a targeted miRNA is introduced into cells. Following the vector gene transcription, the over-expressed synthetic binding sequences occupy the endogenous miRNA in the cells with high affinity blocking miRNA regulation of its target genes. Another approach called the miRNA-mask [84] which uses oligonucleotides perfectly complementary to miRNA binding sites of target mRNAs. The miRNA-mask blocks the access of the miRNA to the binding sequence of the target mRNAs thereby blocking the miRNA-mRNA interaction.

Tumor-targeted delivery and local administration are still major challenges to apply miRNA therapy to the clinic. The possibility of immune response, off-target effects and toxicity of exogenous miRNA mimics or antagonism to normal tissues will have to be taken into account and minimized to a safe level.

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References

1. Meister G, Landthaler M, Patkaniowska A, Dorsett Y, Teng G, Tuschl T (2004) Human Argonaute2 mediates RNA cleavage targeted by miRNAs and siRNAs. Mol Cell 15:185–197
2. Ambros V (2004) The functions of animal microRNAs. Nature 431:350–355
3. Cullen BR (2004) Transcription and processing of human microRNA precursors. Mol Cell 16:861–865
4. Krek A, Grun D, Poy MN, Wolf R, Rosenberg L, Epstein EJ, MacMenamin P, da Piedade I, Gunsalus KC, Stoffel M, Rajewsky N (2005) Combinatorial microRNA target predictions. Nat Genet 37:495–500
5. Cui Q, Yu Z, Purisima EO, Wang E (2006) Principles of microRNA regulation of a human cellular signaling network. Mol Syst Biol 2:46
6. Tili E, Michaille JJ, Gandhi V, Plunkett W, Sampath D, Calin GA (2007) MiRNAs and their potential for use against cancer and other diseases. Future Oncol 3:521–537
7. Calin GA, Croce CM (2006) MicroRNA signatures in human cancers. Nat Rev Cancer 6:857–866
8. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M, Croce CM (2004) Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci USA 101:2999–3004
9. Zhang B, Pan X, Cobb GP, Anderson TA (2007) MicroRNAs as oncogenes and tumor suppressors. Dev Biol 302:1–12
10. Esquela-Kerscher A, Slack FJ. (2006) Oncomirs—microRNAs with a role in cancer. Nat Rev Cancer 6:259–269
11. Cummins JM, Velculescu VE (2006) Implications of micro-RNA profiling for cancer diagnosis. Oncogene 25:6220–6227
12. Takamizawa J, Konishi H, Yanagisawa K, Tomida S, Osada H, Endoh H, Harano T, Yatabe Y, Nagino M, Nimura Y, Mitsudomi T, Takahashi T (2004) Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. Cancer Res 64:3753–3756
13. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, Rassenti L, Kipps T, Negrini M, Bullrich F, Croce CM (2002) 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
14. Yu Z, Wang C, Wang M, Li Z, Casimiro MC, Liu M, Wu K, Whittle J, Ju X, Hyslop T, McCue P, Pestell RG (2008) A cyclin D1/microRNA 17/20 regulatory feedback loop in control of breast cancer cell proliferation. J Cell Biol 182:509–517
15. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Menard S, Palazzo JP, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin GA, Querzoli P, Negrini M, Croce CM (2005) MicroRNA gene expression deregulation in human breast cancer. Cancer Res 65:7065–7070
16. Jiang J, Lee EJ, Gusev Y, Schmittgen TD (2005) Real-time expression profiling of microRNA precursors in human cancer cell lines. Nucleic Acids Res 33:5394–5403

17. Zhang L, Huang J, Yang N, Greshock J, Megraw MS, Giannakakis A, Liang S, Naylor TL, Barchetti A, Ward MR, Yao G, Medina A, O'Brien-Jenkins A, Katsaros D, Hatzigeorgiou A, Gimotty PA, Weber BL, Coukos G (2006) microRNAs exhibit high frequency genomic alterations in human cancer. Proc Natl Acad Sci USA 103:9136–9141
18. Murakami Y, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanoue T, Shimotohno K (2006) Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. Oncogene 25:2537–2545
19. Yanaihara N, Caplen N, Bowman E, Seike M, Kumamoto K, Yi M, Stephens RM, Okamoto A, Yokota J, Tanaka T, Calin GA, Liu CG, Croce CM, Harris CC (2006) Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 9:189–198
20. Porkka KP, Pfeiffer MJ, Waltering KK, Vessella RL, Tammela TL, Visakorpi T (2007) MicroRNA expression profiling in prostate cancer. Cancer Res 67:6130–6135
21. Gottardo F, Liu CG, Ferracin M, Calin GA, Fassan M, Bassi P, Sevignani C, Byrne D, Negrini M, Pagano F, Gomella LG, Croce CM, Baffa R (2007) Micro-RNA profiling in kidney and bladder cancers. Urol Oncol 25:387–392
22. Schepeler T, Reinert JT, Ostenfeld MS, Christensen LL, Silahtaroglu AN, Dyrskjot L, Wiuf C, Sorensen FJ, Kruhoffer M, Laurberg S, Kauppinen S, Orntoft TF, Andersen CL (2008) Diagnostic and prognostic microRNAs in stage II colon cancer. Cancer Res 68:6416–6424
23. Pestell RG, Albanese C, Reutens AT, Segall JE, Lee RJ, Arnold A (1999) The cyclins and cyclin-dependent kinase inhibitors in harmonal regulation of prolifertion and differentiation. Endocr Rev Aug 20(4):501–534
24. Fu M, Wang C, Li Z, Sakamaki T, Pestell RG (2004) Minireview: Cyclin D1: Normal and abnormal functions. Endocrinology 145:5439–5447
25. Jiang W, Kahn SM, Tomita N, Zhang YJ, Lu SH, Weinstein IB (1992) Amplification and expression of the human cyclin D gene in esophageal cancer. Cancer Res 52:2980–2983
26. Lazzereschi D, Sambuco L, Carnovale Scalzo C, Ranieri A, Mincione G, Nardi F, Colletta G (1998) Cyclin D1 and Cyclin E expression in malignant thyroid cells and in human thyroid carcinomas. Int J Cancer 76:806–811
27. O'Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT (2005) C-Myc-regulated microRNAs modulate E2F1 expression. Nature 435:839–843
28. Lee RJ, Albanese C, Fu M, D'Amico M, Lin B, Watanabe G, Haines GK 3rd, Siegel PM, Hung MC, Yarden Y, Horowitz JM, Muller WJ, Pestell RG (2000) Cyclin D1 is required for transformation by activated Neu and is induced through an E2F-dependent signaling pathway. Mol Cell Biol Jan 20(2):672–683
29. Lu Y, Thomson JM, Wong HY, Hammond SM, Hogan BL (2007) Transgenic over-expression of the microRNA miR-17-92 cluster promotes proliferation and inhibits differentiation of lung epithelial progenitor cells. Dev Biol 310:442–453
30. Miller TE, Ghoshal K, Ramaswamy B, Roy S, Datta J, Shapiro CL, Jacob S, Majumder S (2008) MicroRNA-221/222 confers tamoxifen resistance in breast cancer by targeting p27Kip1. J Biol Chem 283:29897–29903
31. Bonci D, Coppola V, Musumeci M, Addario A, Giuffrida R, Memeo L, D'Urso L, Pagliuca A, Biffoni M, Labbaye C, Bartucci M, Muto G, Peschle C, De Maria R (2008) The miR-15a-miR-16-1 cluster controls prostate cancer by targeting multiple oncogenic activities. Nat Med 14:1271–1277
32. Bottoni A, Piccin D, Tagliati F, Luchin A, Zatelli MC, degli Uberti EC (2005) MiR-15a and miR-16-1 down-regulation in pituitary adenomas. J Cell Physiol 204:280–285
33. Deshpande A, Pastore A, Deshpande AJ, Zimmermann Y, Hutter G, Weinkauf M, Buske C, Hiddemann W, Dreyling M (2009) 3'UTR mediated regulation of the cyclin D1 proto-oncogene. Cell Cycle 8:3584–3592
34. Liu Q, Fu H, Sun F, Zhang H, Tie Y, Zhu J, Xing R, Sun Z, Zheng X (2008) MiR-16 family induces cell cycle arrest by regulating multiple cell cycle genes. Nucleic Acids Res 36:5391–5404
35. Yu Z, Baserga R, Chen L, Wang C, Lisanti MP, Pestell RG (2010) MicroRNA, cell cycle, and human breast cancer. Am J Pathol 176:1058–1064

36. Kim YK, Yu J, Han TS, Park SY, Namkoong B, Kim DH, Hur K, Yoo MW, Lee HJ, Yang HK, Kim VN (2009) Functional links between clustered microRNAs: suppression of cell-cycle inhibitors by microRNA clusters in gastric cancer. Nucleic Acids Res 37:1672–1681
37. Schetter AJ, Leung SY, Sohn JJ, Zanetti KA, Bowman ED, Yanaihara N, Yuen ST, Chan TL, Kwong DL, Au GK, Liu CG, Calin GA, Croce CM, Harris CC (2008) MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. JAMA 299:425–436
38. Yang N, Kaur S, Volinia S, Greshock J, Lassus H, Hasegawa K, Liang S, Leminen A, Deng S, Smith L, Johnstone CN, Chen XM, Liu CG, Huang Q, Katsaros D, Calin GA, Weber BL, Butzow R, Croce CM, Coukos G, Zhang L (2008) MicroRNA microarray identifies Let-7i as a novel biomarker and therapeutic target in human epithelial ovarian cancer. Cancer Res 68:10307–10314
39. Yu F, Yao H, Zhu P, Zhang X, Pan Q, Gong C, Huang Y, Hu X, Su F, Lieberman J, Song E (2007) let-7 regulates self renewal and tumorigenicity of breast cancer cells. Cell 131: 1109–1123
40. Mayr C, Hemann MT, Bartel DP. (2007) Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. Science 315:1576–1579
41. Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, Labourier E, Reinert KL, Brown D, Slack FJ (2005) RAS is regulated by the let-7 microRNA family. Cell 120:635–647
42. Tsang WP, Kwok TT (2008) Let-7a microRNA suppresses therapeutics-induced cancer cell death by targeting caspase-3. Apoptosis 13:1215–1222
43. Sampson VB, Rong NH, Han J, Yang Q, Aris V, Soteropoulos P, Petrelli NJ, Dunn SP, Krueger LJ (2007) MicroRNA let-7a down-regulates MYC and reverts MYC-induced growth in Burkitt lymphoma cells. Cancer Res 67:9762–9770
44. Schultz J, Lorenz P, Gross G, Ibrahim S, Kunz M (2008) MicroRNA let-7b targets important cell cycle molecules in malignant melanoma cells and interferes with anchorage-independent growth. Cell Res 18:549–557
45. Johnson CD, Esquela-Kerscher A, Stefani G, Byrom M, Kelnar K, Ovcharenko D, Wilson M, Wang X, Shelton J, Shingara J, Chin L, Brown D, Slack FJ (2007) The let-7 microRNA represses cell proliferation pathways in human cells. Cancer Res 67:7713–7722
46. Garzon R, Heaphy CE, Havelange V, Fabbri M, Volinia S, Tsao T, Zanesi N, Kornblau SM, Marcucci G, Calin GA, Andreeff M, Croce CM (2009) MicroRNA 29b functions in acute myeloid leukemia. Blood 114:5331–5341
47. Wang H, Garzon R, Sun H, Ladner KJ, Singh R, Dahlman J, Cheng A, Hall BM, Qualman SJ, Chandler DS, Croce CM, Guttridge DC (2008) NF-kappaB-YY1-miR-29 regulatory circuitry in skeletal myogenesis and rhabdomyosarcoma. Cancer Cell 14:369–381
48. Xiong Y, Fang JH, Yun JP, Yang J, Zhang Y, Jia WH, Zhuang SM (2010) Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma. Hepatol 51:836–845
49. Zhao JJ, Lin J, Lwin T, Yang H, Guo J, Kong W, Dessureault S, Moscinski LC, Rezania D, Dalton WS, Sotomayor E, Tao J, Cheng JQ (2010) microRNA expression profile and identification of miR-29 as a prognostic marker and pathogenetic factor by targeting CDK6 in mantle cell lymphoma. Blood 115:2630–2639
50. He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, Xue W, Zender L, Magnus J, Ridzon D, Jackson AL, Linsley PS, Chen C, Lowe SW, Cleary MA, Hannon GJ (2007) A microRNA component of the p53 tumour suppressor network. Nature 447:1130–1134
51. Tarasov V, Jung P, Verdoodt B, Lodygin D, Epanchintsev A, Menssen A, Meister G, Hermeking H (2007) Differential regulation of microRNAs by p53 revealed by massively parallel sequencing: miR-34a is a p53 target that induces apoptosis and G1-arrest. Cell Cycle 6:1586–1593
52. Sun F, Fu H, Liu Q, Tie Y, Zhu J, Xing R, Sun Z, Zheng X (2008) Downregulation of CCND1 and CDK6 by miR-34a induces cell cycle arrest. FEBS Lett 582:1564–1568

53. Corney DC, Flesken-Nikitin A, Godwin AK, Wang W, Nikitin AY (2007) MicroRNA-34b and MicroRNA-34c are targets of p53 and cooperate in control of cell proliferation and adhesion-independent growth. Cancer Res 67:8433–8438
54. Braun CJ, Zhang X, Savelyeva I, Wolff S, Moll UM, Schepeler T, Orntoft TF, Andersen CL, Dobbelstein M (2008) p53-Responsive micrornas 192 and 215 are capable of inducing cell cycle arrest. Cancer Res 68:10094–10104
55. Si ML, Zhu S, Wu H, Lu Z, Wu F, Mo YY (2007) miR-21-mediated tumor growth. Oncogene 26:2799–2803
56. Frankel LB, Christoffersen NR, Jacobsen A, Lindow M, Krogh A, Lund AH (2008) 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
57. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T (2007) MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology 133:647–658
58. Zhu S, Si ML, Wu H, Mo YY (2007) MicroRNA-21 targets the tumor suppressor gene tropomyosin 1 (TPM1). J Biol Chem 282:14328–14336
59. Scott GK, Mattie MD, Berger CE, Benz SC, Benz CC (2006) Rapid alteration of microRNA levels by histone deacetylase inhibition. Cancer Res 66:1277–1281
60. Mertens-Talcott SU, Chintharlapalli S, Li X, Safe S (2007) The oncogenic microRNA-27a targets genes that regulate specificity protein transcription factors and the G2-M checkpoint in MDA-MB-231 breast cancer cells. Cancer Res 67:11001–11011
61. Kong W, He L, Coppola M, Guo J, Esposito NN, Coppola D, Cheng JQ (2010) MicroRNA-155 regulates cell survival, growth, and chemosensitivity by targeting FOXO3a in breast cancer. J Biol Chem 285:17869–17879
62. Metzler M, Wilda M, Busch K, Viehmann S, Borkhardt A (2004) High expression of precursor microRNA-155/BIC RNA in children with Burkitt lymphoma. Genes Chromosomes Cancer 39:167–169
63. Gironella M, Seux M, Xie MJ, Cano C, Tomasini R, Gommeaux J, Garcia S, Nowak J, Yeung ML, Jeang KT, Chaix A, Fazli L, Motoo Y, Wang Q, Rocchi P, Russo A, Gleave M, Dagorn JC, Iovanna JL, Carrier A, Pebusque MJ, Dusetti NJ (2007) Tumor protein 53-induced nuclear protein 1 expression is repressed by miR-155, and its restoration inhibits pancreatic tumor development. Proc Natl Acad Sci USA 104:16170–16175
64. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF (2003) Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 100:3983–3988
65. Gupta PB, Chaffer CL, et al (2009) Cancer stem cells: mirage or reality? Nature Med 15:1010–1012
66. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, Dirks PB (2003) Identification of a cancer stem cell in human brain tumors. Cancer Res 63:5821–5828
67. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, Minden M, Paterson B, Caligiuri MA, Dick JE (1994) A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 367:645–648
68. Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, De Maria R (2007) Identification and expansion of human colon-cancer-initiating cells. Nature 445: 111–115
69. Li C, Heidt DG, Dalerba P, Burant CF, Zhang L, Adsay V, Wicha M, Clarke MF, Simeone DM (2007) Identification of pancreatic cancer stem cells. Cancer Res 67:1030–1037
70. Ginestier C, Hur MH, Charafe-Jauffret E, Monville F, Dutcher J, Brown M, Jacquemier J, Viens P, Kleer CG, Liu S, Schott A, Hayes D, Birnbaum D, Wicha MS, Dontu G (2007) ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 1:555–567
71. Velasco-Velázquez MA, Yu Z, Jiao X, et al (2009) Cancer stem cells and the cell cycle: targeting the drive behind breast cancer. Expert Rev Anticancer Ther 9:275–9

72. Qian S, Ding JY, Xie R, An JH, Ao XJ, Zhao ZG, Sun JG, Duan YZ, Chen ZT, Zhu B (2008) MicroRNA expression profile of bronchioalveolar stem cells from mouse lung. Biochem Biophys Res Commun 377:668–673
73. Shimono Y, Zabala M, Cho RW, Lobo N, Dalerba P, Qian D, Diehn M, Liu H, Panula SP, Chiao E, Dirbas FM, Somlo G, Pera RA, Lao K, Clarke MF (2009) Downregulation of miRNA-200c links breast cancer stem cells with normal stem cells. Cell 138:592–603
74. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, Vadas MA, Khew-Goodall Y, Goodall GJ (2008) The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nat Cell Biol 10:593–601
75. Huang Q, Gumireddy K, Schrier M, le Sage C, Nagel R, Nair S, Egan DA, Li A, Huang G, Klein-Szanto AJ, Gimotty PA, Katsaros D, Coukos G, Zhang L, Pure E, Agami R (2008) The microRNAs miR-373 and miR-520c promote tumour invasion and metastasis. Nat Cell Biol 10:202–210
76. Yu Z, Willmarth NE, Zhou J, Katiyar S, Wang M, Liu Y, McCue PA, Quong AA, Lisanti MP, Pestell RG (2010) MicroRNA 17/20 inhibits cellular invasion and tumor metastasis in breast cancer by heterotypic signaling. Proc Natl Acad Sci USA 107:8231–8236
77. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR (2005) MicroRNA expression profiles classify human cancers. Nature 435:834–838
78. Kumar MS, Lu J, Mercer KL, Golub TR, Jacks T (2007) Impaired microRNA processing enhances cellular transformation and tumorigenesis. Nat Genet 39:673–677
79. Bader AG, Brown D, Winkler M (2010) The promise of microRNA replacement therapy. Cancer Res 70:7027–7030
80. Trang P, Medina PP, Wiggins JF, Ruffino L, Kelnar K, Omotola M, Homer R, Brown D, Bader AG, Weidhaas JB, Slack FJ (2010) Regression of murine lung tumors by the let-7 microRNA. Oncogene 29:1580–1587
81. Wiggins JF, Ruffino L, Kelnar K, Omotola M, Patrawala L, Brown D, Bader AG (2010) Development of a lung cancer therapeutic based on the tumor suppressor microRNA-34. Cancer Res 70:5923–5930
82. Kota J, Chivukula RR, O'Donnell KA, Wentzel EA, Montgomery CL, Hwang HW, Chang TC, Vivekanandan P, Torbenson M, Clark KR, Mendell JR, Mendell JT (2009) Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. Cell 137:1005–1017
83. Ebert MS, Neilson JR, Sharp PA (2007) MicroRNA sponges: competitive inhibitors of small RNAs in mammalian cells. Nat Methods 4:721–726
84. Choi WY, Giraldez AJ, Schier AF (2007) Target protectors reveal dampening and balancing of Nodal agonist and antagonist by miR-430. Science 318:271–274

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