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MicroRNA-based Cancer Therapeutics: Big Hope from Small RNAs

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Abstract

Tremendous progress has been made during the last few years in identification of novel tumor-associated microRNAs and experimental validation of their cancer relevant gene targets. Indeed, these small non-coding RNAs are now known to modulate many biological pathways related to cancer progression, metastasis and therapy-resistance. Therefore, modulating miRNA functions may provide novel therapeutic opportunities for cancer treatment. This article reviews recent literature on the role of miRNAs in cancer with an emphasis on their potential as cancer therapeutics.

Keywords

MicroRNAs; Small RNAs; Cancer; Therapeutics

Introduction

MicroRNAs (miRNAs or miRs) have received significant attention as a new class of noncoding-RNAs engaged in the regulation of gene expression. miRNAs are short 19–25nt stretches of RNA that bind to the target mRNAs and suppress their translation or initiate decay (1). More than 500 different miRNAs have been identified in humans and their total number is predicted to exceed 1000 (1;2). Despite this large number of identified miRNAs, the target mRNAs and the biological function have been ascribed to only a few of them. With increasing interest and research investigations, it is now becoming evident that miRNAs exhibit differential expression in several human diseases, including cancer and play important roles in the disease processes (3). Some of the miRNAs have clearly been shown to influence the development and progression of cancer (3). Therefore, identification of novel differentially-expressed miRNAs, establishing their cancer-associated functions and developing ways to modulate their activities may yield powerful therapeutic strategies against cancer. This review summarizes some of the recent and significant findings on role of miRNAs in cancer development with a focus on their future in cancer therapeutics.

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Conflicts of Interest

No potential conflicts of interest to disclose.

MicroRNAs

Biogenesis and mechanism of gene silencing

Biogenesis of miRNAs begins with transcription by RNA polymerase II or RNA polymerase III, producing primary miRNA (pri-miRNA) (4). Pri-miRNAs contain a single or multiple (miRNA cluster) folded hairpin stem structure(s) with flanking single-stranded upstream and downstream regions (Figure 1). Following synthesis, pri-miRNA is first processed inside the nucleus by RNase III (Drosha) and the DGCR8 (DiGeorge critical region 8) to yield a ~70 nucleotides long precursor miRNA (pre-miRNA). Pre-miRNA is transported to the cytoplasm by the nuclear export factor Exportin-5/Ran-GTP, where it is processed through a series of cuts by RNase III endonuclease, Dicer/TRBP and Ago2 to generate a mature 17–25 bp miRNA duplex (4). The miRNA duplex is unwound into a mature single-stranded miRNA (one of the strand) by a helicase, which then enters into the RNA-induced silencing complex (RISC) and directs the complex to target mRNA through a poorly defined mechanism (5) (Figure 1). It is commonly accepted that mature miRNAs regulate gene expression by binding to the 3'-untranslated region (3'-UTR) of target mRNA, causing degradation of mRNA or inhibition of their translation (4;5). The specificity in choosing target transcripts is mainly decided by sequence complementarity between mRNA target sites and the nucleotide sequence from position 2 to 8 at the 5' end of miRNAs known as "Seed Region". Although base pairing to the 3' end of miRNA is thought to be less important in target recognition, it may contribute in target selection especially when sites have weaker miRNA seed matches (6).

MicroRNAs in cancer

Croce and colleagues, for the first time, reported a link between miRNAs and cancer by mapping the genomic locus of miR15 and miR16 to chromosome 13q14, a region deleted in majority of B cell chronic lymphocytic leukemias (B-CLL) (7). Since then, studies in a variety of human tumors have shown that miRNAs are frequently associated with sites of chromosomal instability or amplification (8). Furthermore, many recent experimental and clinical studies have revealed that the aberrant expression of miRNAs is associated with the stage, progression, and metastasis of cancers (8,9). It has been shown that miRNAs can function as tumor promoters (oncomirs) or tumor suppressors (anti-oncomirs) (3,10). Moreover, miRNAs are also shown to be implicated in cancer stem cells (CSCs) and epithelial-mesenchymal transition (EMT), which are critically associated with cancer metastasis and drug resistance (8,11).

Oncogenic microRNAs (Oncomirs)

The "oncomirs" promote tumor development by negatively inhibiting tumor suppressor genes and/or genes that control cell differentiation or apoptosis. Oncomirs are significantly overexpressed in various tumors because of gene amplification, epigenetic mechanisms or transcriptional dysregulation (10). miR-17-92 cluster is a typical example, which is located at chromosome 13q31, a region amplified in lung and other malignancies (12). Myc-induced up-regulation of miR-17-92 cluster has been shown to enhance tumorigenesis and angiogenesis (13). Recent studies also revealed that miR-17-92 was upregulated in sonic hedgehog-driven medulloblastomas and induced by N-myc in sonic hedgehog-treated cerebellar neural precursors (14,15). Among others oncogenic miRNAs, miR-21 has been shown to promote apoptosis through activation of caspases in human glioblastoma cells (16). In breast cancer cells, silencing of miR-21 inhibited cell growth *in vitro* and *in vivo* by causing downregulation of Bcl-2 and induction of apoptosis (17). Among the experimentally validated targets of miR-21 are Pdcd4, bone morphogenetic protein receptor II (BMPRII) and LRRFIP1 (an inhibitor of NF- κ B signaling) (18–20). miRNA expression profiling have

reported increased expression of miR-155 in various cancers. Its expression was significantly correlated with poor survival in pancreatic cancer patients (21). In another study, transfection of anti-miR-155 oligonucleotides into pancreatic cancer induced the expression of tumor suppressor protein 53-induced nuclear protein 1 (TP53INP1) and enhanced apoptosis (22). miR-372 and miR-373 are two additional examples of oncogenic miRNAs that are shown to promote cell proliferation and tumor development by neutralizing p53-mediated CDK inhibition, possibly through direct targeting of the tumor suppressor gene LATS2 (23). Further research is likely to add many more miRNAs to the growing list of oncomirs.

Tumor suppressor miRNAs (Anti-oncomirs)

There are several miRNAs that are considered as tumor suppressors, viz. let-7, miR-17-5p, miR-29, miR-34, miR-127 etc (10,24). Indeed, the earliest miRNAs identified to be tumor-associated (miR-15 and miR-16) were from this class (7), which are now experimentally shown to possess anti-oncogenic activity (25). miR-15/16 induce apoptosis by negatively regulating the expression of anti-apoptotic gene, BCL2 (26). In another study, miR-16 is shown to suppress the growth of prostate cancer cells by regulating the expression of CDK1 and CDK2, which are associated with cell cycle control and proliferation (27). It has also been demonstrated that miR-15a and miR-16-1 cluster in prostate cancer cells targets CCND1 (encoding cyclin D1) and WNT3A, and thus impact survival, proliferation and invasion (28). Among the most studied tumor suppressor miRNAs are the members of let-7 family. Expression of let-7 miRNAs is downregulated in various cancers and they are good candidates as diagnostic and prognostic biomarkers (10,29). Expression of let-7 is frequently decreased in lung cancer and forced expression of let-7 in A549 lung adenocarcinoma cell line inhibited cancer cell growth (24). RAS and MYC are the direct targets of let-7 (29), indicating its pathogenic potential in many other RAS and MYC-driven cancers. miR-34a is another miRNA in this category that participates in p53 tumor suppressor network and have been shown to be directly transactivated by p53 (30,31). Overexpression of miR-34a induces apoptosis and alters the expression of several genes related to cell cycle progression, apoptosis, DNA repair, and angiogenesis (30). In a recent study, it was also shown that miR-34a inhibited human pancreatic cancer tumor-initiating cells and restored the tumor-suppressor function of p53 in p53-deficient human pancreatic cancer cells (31).

MicroRNAs in cancer stem cells and epithelial to mesenchymal transition

Cancer stem cells (CSCs) are considered that rare subpopulation of cancer cells, which is responsible for tumor heterogeneity, maintenance and therapy-resistance (32). Therefore, efforts are now being made to understand the mechanisms that sustain the 'stemness' of CSCs. It was shown that induction of epithelial to mesenchymal transition (EMT) stimulated cultured breast cells to adopt the characteristics of stem cells (33). During EMT, cells attain a migratory phenotype by losing the cell-cell and cell-extracellular matrix interactions and literature suggests an important role of EMT in cancer progression and metastasis. Recent emerging evidence indicate a critical role of miRNAs in the maintenance of normal and cancer stem cells and acquisition of EMT phenotype (34,35). Indeed, some miRNAs, such as let-7, miR 30, miR-34a, miR 155, miR 370 have been shown to be implicated in self-renewal, differentiation and survival of CSCs (31,34,36). Let-7 is reported to interact with MYC and LIN-28 to control stem cell properties (37). In another study, a drastically reduced expression of let-7 was reported in breast cancer stem cells, which increased as the cells differentiated (38). It was shown that let-7 regulated stem cell properties and tumorigenic behavior of cancer cells by targeting the expression of multiple genes, including H-RAS and HMGA-2 (38). In additional studies, certain miRNAs have been shown to act as the regulators of CSCs and EMT by regulating the expression of BMI1, E-cadherin and other proteins (35). In a recent study, it was reported that the induction of members of miR-200

and let-7 families by natural agents led to the reversal of EMT in pancreatic cancer cells (39). The expression of miR-200 and let-7 family miRNAs was downregulated in gemcitabine-resistant pancreatic cancer cell lines with more mesenchymal characteristics. Ectopic expression of miR-200a, miR-200b, and miR-200c pre-miRNAs resulted in the acquisition of epithelial characteristics and enhanced drug-sensitivity (39). Another study from the same group in prostate cancer cells reported that re-expression of miR-200b led to the reversal of EMT along with the downregulation of ZEB1, ZEB2 and Slug expression (40).

MicroRNAs as novel cancer therapeutics

In consideration of the fact that miRNAs involve in tumor initiation, progression and metastasis, their targeting is expected to emerge as an effective therapeutic option for cancer treatment. Plausible approaches for therapy would include achieving “gain” or “loss” of miRNA functions in the cancer cells (Figure 2). Since many miRNAs have been identified to impart tumor suppressive effects, restoring their expression (endogenously or exogenously) may yield therapeutic effects. In an earlier study, ectopic overexpression of let-7 tumor suppressor miRNA was shown to inhibit the growth of lung, liver and pancreatic cancer cells (24,29). Furthermore, systemic administration of miR-26a using adeno-associated virus (AAV) in an animal model of hepatocellular carcinoma (HCC) also inhibited tumor progression without toxicity (41). This study not only provided an important target miRNA with tumor suppressive activity, but also indicated that adenoviral vector-based delivery could be a clinically feasible approach. In other reports, synthetic miRNA mimics have also been used to restore miRNA function within the tumor cell (42). For oncogenic miRNAs, multiple approaches have been designed and tested to achieve their downregulation. These approaches include the use of anti-miRNA oligonucleotides (AMOs), small molecule inhibitors, miRNA sponges and miRNA masking. AMOs can block the interactions between miRNA and its target mRNAs through competitive inhibition of base-pairing (43). AMOs against miR-21 were shown to inhibit the growth of MCF-7 cells *in vivo* (17). Other study has shown that intravenous administration of AMOs against miR-16, miR-122, miR-192 and miR-194 in animals offer efficient and sustained silencing of corresponding miRNAs (44). The downregulation of miRNAs can also be achieved by targeting their biogenesis. In a recent study, several small organic molecules were screened for their potential to block miR-21 function and azobenzene was identified as an efficient inhibitor of miR-21 expression (45). Another strategy that has been tested to block miRNA function is the use of synthetic mRNA containing multiple pairing sites for endogenous miRNA. Such synthetic mRNAs, referred as miRNA sponges, function by sucking up the target miRNAs and thus blocking their regulatory function in the cell (46). Some recent studies have also employed an approach of using target protectors (miR-masks) (47,48). miR-masks are like AMOs, however, they do not directly interact with its target miRNA but instead bind to the pairing site of miRNAs in the 3' UTR of the target mRNA by fully complementary mechanism. In a rat model, miR-masks complementary to HCN2 and HCN4 genes masked the actions of their respective targeting miRNAs, miR-1 and miR-133 (48). In another study, protection of squint or lefty mRNAs from miR-430 was also reported (47). These studies suggest that silencing or restoration of miRNA function can serve as a promising therapeutic strategy for cancer treatment. Furthermore, as miRNAs are also associated with chemo- and radio-sensitization of cancer cells (19;49), a combination approach can also be developed for improved therapeutic outcome.

Conclusion and perspectives

Emergence of miRNAs as a new class of gene regulators and their proven role in cancer progression has opened new avenues for therapeutic discovery. Interest in miRNAs is now

more than ever and the literature is getting enriched rapidly with reports on novel miRNAs, their validated gene targets and the development of miRNA-based therapeutics. The realization of a miRNA-based therapeutic approach in clinics; however, may still be far from sight and several hindrances pertaining to the stability, specificity and delivery of short oligonucleotides need to be overcome. Nonetheless, the use of LNA (locked nucleic acid) technology has presented a breakthrough and a phase I clinical trial with LNA-antimiR-122 has already been initiated based on exciting preliminary data in non-human primates (50). Also, advances have been made in the delivery systems and the systemic administration of miRNA using adeno-associated virus (AAV) has been tested in pre-clinical model (41). Similarly, cationic liposomes or polymer-based nanoparticle formulations can be developed to achieve the delivery of miRNA mimics and tested for therapeutic efficacy. With increasing interest, research progress in miRNA functions and technological advancements, miRNA-based therapeutics may create a paradigm-shift in medicine and pharmaceutical industry.

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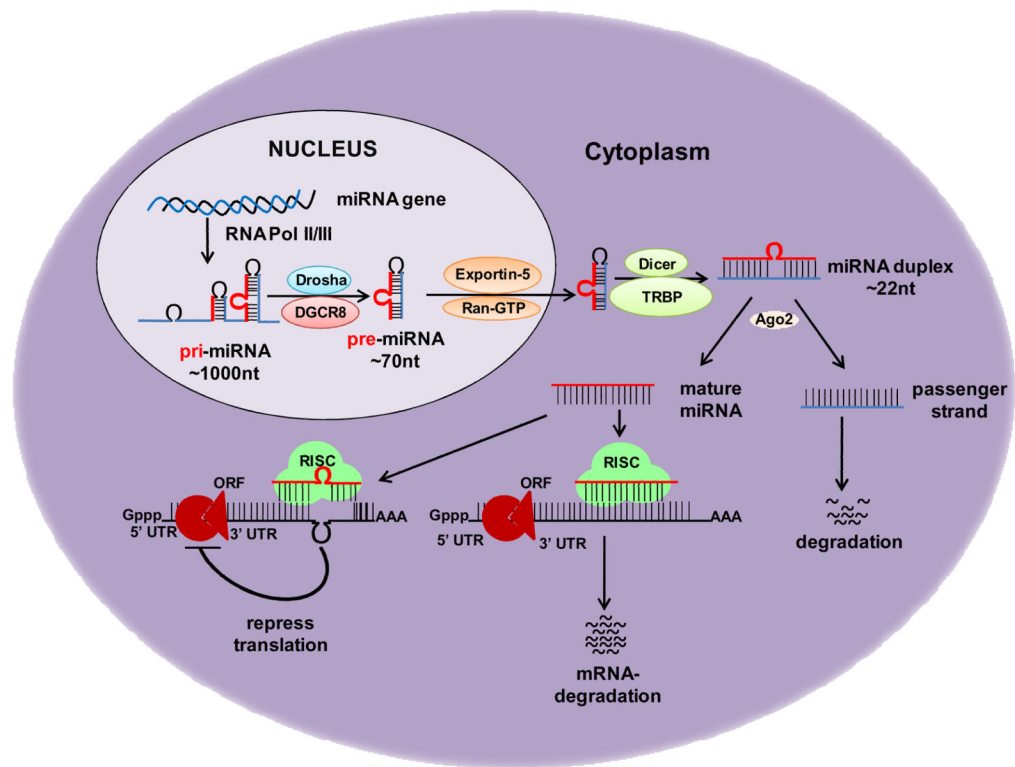


Figure 1. MicroRNA biogenesis and mechanisms of gene silencing

MicroRNA (miRNA) genes are generally transcribed by RNA polymerase II/III in nucleus to form large primary transcript (pri-miRNA). These pri-miRNA transcripts are processed to release the ~70-nucleotide hairpin RNA known as precursor-miRNA (pre-miRNA), which is transported to the cytoplasm and undergoes another processing to yield a transient ~22-nucleotide RNA duplex. RNA duplex is unwound into a mature single-stranded miRNA, and loaded into RNA-induced silencing complex (RISC). miRNA then binds to complementary sites in the 3'-untranslated region (3'-UTR) of target mRNA and regulate its expression either by causing degradation of mRNA or repression of their translation, depending on the degree of complementarity between the miRNA and its target.

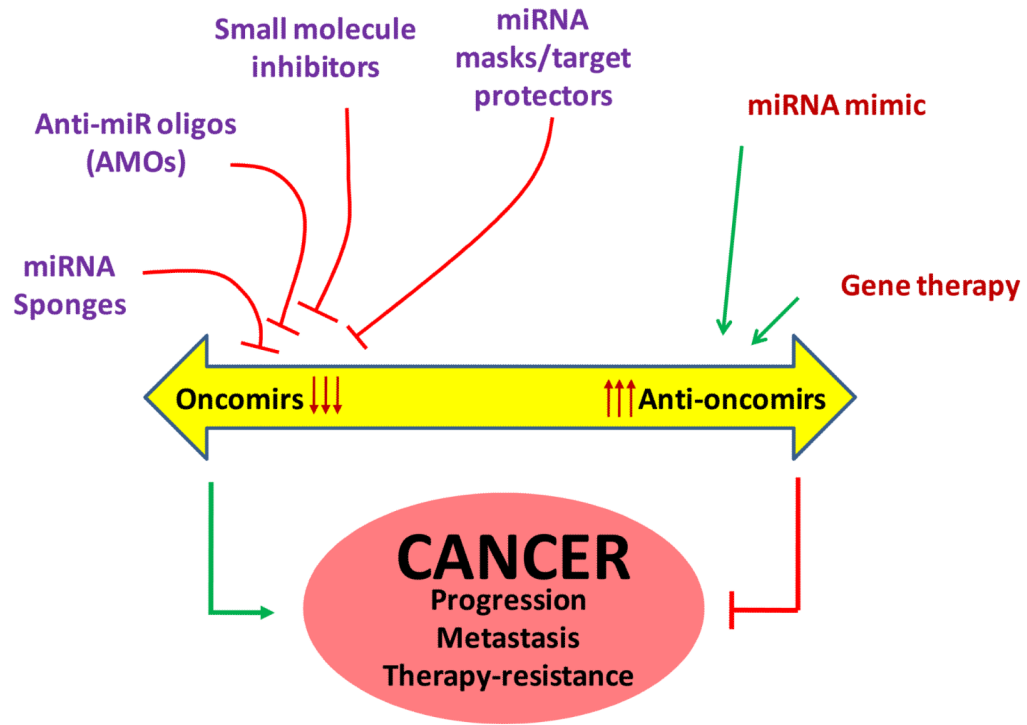


Figure 2. miRNA-based therapeutic strategies against cancer

Inhibiting the function of oncomirs by use of anti-miR oligonucleotides (AMOs), small molecule inhibitors, miRNA sponges and miRNA masks/target protectors, and promoting the activity of anti-oncomirs through gene therapy or delivery of miRNA mimics can serve as novel therapeutic options against cancer.