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REVIEW ARTICLE

Therapeutic microRNAs in human cancer

Gizem Ors-Kumoglu · Sultan Gulce-Iz · Cigir Biray-Avci

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Abstract MicroRNAs (miRNAs) are RNA molecules at about 22 nucleotide in length that are non-coding, which regulate gene expression in the post-transcriptional level by performing degradation or blocks translation of the target mRNA. It is known that they play roles in mechanisms such as metabolic regulation, embryogenesis, organogenesis, differentiation and growth control by providing post-transcriptional regulation of gene expression. With these properties, miRNAs play important roles in the regulation of biological processes such as proliferation, differentiation, apoptosis, drug resistance mechanisms in eukaryotic cells. In addition, there are miRNAs that can be used for cancer therapy. Tumor cells and tumor microenvironment have different miRNA expression profiles. Some miRNAs are known to play a role in the onset and progression of the tumor. miRNAs with oncogenic or tumor suppressive activity specific to different cancer types are still being investigated. This review summarizes the role of miRNAs in tumorigenesis, therapeutic strategies in human cancer and current studies.

Keywords Cancer therapy · miRNA mimic · miRNA antagonists · miRNA sponges · miRNA masking

Abbreviations

miRNA	MicroRNA
RISC	RNA-induced silencing complex
oncomiR	Oncogenic miRNA
tsmiR	Tumor suppressor miRNA
UTR	Unstranslated region(s)
anti-miR(s)	Anti-miRNA oligonucleotides
NSCLC	Non-small-cell lung cancer
antagomiR(s)	miRNA antagonists
PTEN	Phosphatase and tensin homolog
VEGF	Vascular epidermal growth factor
SOCS1	Suppressor of cytokine signaling 1
AMOs	Anti-miRNA oligonucleotides
HCN1	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 1

Introduction

MiRNAs have gained rapid diagnostic and therapeutic value by providing unique expression profiles and high

G. Ors-Kumoglu (✉) · S. Gulce-Iz
Department of Bioengineering, Faculty of Engineering, Ege University, Izmir, Turkey
e-mail: gizemors1@gmail.com

S. Gulce-Iz
Biomedical Technologies Graduate Programme, Institute of Natural and Applied Sciences, Ege University, Izmir, Turkey

C. Biray-Avci
Department of Medical Biology, Faculty of Medicine, Ege University, Izmir, Turkey

stability in biological samples that have multiple targets or are involved in many cancer-related pathways. In general, the therapeutic side of miRNAs is provided by inhibiting oncogenic miRNAs or by regenerating tumor suppressor miRNAs. The first miRNA synthesized by RNA polymerase II is about 700 bases in length (Bartel 2004). These miRNAs, called pri-miRNAs, are transcribed in the nucleus, and then Drosha is a member of the RNAase III, cleaves this pri-miRNA from both ends with complex endonuclease activity (Denli et al. 2004). As a result of this process, pri-miRNA is called pre-miRNA and its length is about 70–100 bases. Pre-miRNAs are transferred from the nucleus to the cytoplasm by a carrier protein called "exportin-5" (Bartel 2004; Cullen 2004; Gregory et al. 2004; Lund et al. 2004).

The pre-miRNAs transferred to the cytoplasm are linked to the "Dicer" (RNAse III member) molecule. Dicer cleaves pre-miRNA's stem-loop to yield shorter, double-stranded miRNAs (duplex miRNAs). These miRNAs are 21–23 nucleotides long with two unpaired 3′ nucleotides at each end. But only one of the strands is bound to RISC (RNA-stimulated silencing complex) (Lund et al. 2004; Pillai et al. 2007).

The RISC-miRNA complex matches the transcript in the 3′ UTR region of the target mRNA, so that the translation of the transcripts is repressed through different mechanisms. With this repression event, oncomiRs play roles such as inhibition of metastasis, induction of metastasis, drug resistance mechanisms (Chen et al. 2007; Shenouda and Alahari 2009; Shi et al. 2010). However, some miRNAs have been shown to work as tumor suppressor in breast cancer (Esquela-Kerscher and Slack 2006), lung cancer (Zhang et al. 2013a, b), colorectal cancer (Liu and Chen 2010) and ovarian cancer (Kinose et al. 2014), while others have been shown to have oncogenic properties with profiling studies.

One of the most attractive features of miRNAs as therapeutic agents is their ability to target multiple molecules. This advantage is highly effective in regulating different biological cell processes related to normal tissue and tumor tissue. Moreover, miRNAs have many roles in cancer progression, such as proliferation, apoptosis, cell cycle arrest (Park et al. 2011; Wang et al. 2014; Qin et al. 2016; Cui et al. 2018), migration, invasion, metastasis (Zhang et al. 2012; Mohammadi-Yeganeh et al. 2016; Lei et al. 2017), cytokine secretion (Yu et al. 2013; Mignacca et al. 2016; Muhammad et al. 2016), T cell differentiation (Jeker and Bluestone 2013; Kroesen et al. 2015; Tao et al. 2018), drug resistance (Li et al. 2015; Yang et al. 2015a; Zhao et al. 2017; Chen et al. 2018b), and chemo-sensitivity (Giunti et al. 2015; Li et al. 2017a; Chen et al. 2018b) by activating molecular target. This knowledges suggests that miRNAs can be used as adjunct vehicles for cancer progression (Shenouda and Alahari 2009; Babashah and Soleimani 2011; Garofalo and Croce 2013; Cheng et al. 2014) (Table 1).

Therapeutic strategies

In generally, there are two basic strategies for therapeutic approaches to regulate miRNA expressions. These strategies involve the use of oligonucleotides or virus-based constructs to inhibit the expression of an oncogenic miRNA or to reactivate a tumor suppressor miRNA that has been lost in cancer. As shown in Fig. 1, there are four different mechanisms that are supposed to stop the onset and progression of the tumor. miRNA mimic, anti-miRNA oligonucleotides (anti-miRs), miRNA sponges, and miRNA masking treatment approaches have been described in detail.

miRNA mimics approaches

MiRNA mimic technology (miR-Mimic) is an approach based on gene silencing. After transfection into cells, they act as mature endogenous miRNAs. miR-Mimics are chemically synthesized, double-stranded RNAs. The sequence at the 5′ end of these RNA fragments is designed to be partially complementary to the sequence at the 3′ UTR of the target gene (Ji et al. 2017). A lost or downregulated tumor suppressor miRNA (tsmiR) activity can be restored using miRNA mimics (Bader et al. 2011). This method has been studied in many types of cancer and successful progress has been recorded (Table 2).

Overexpression of miR-892b mediated by mimics in breast cancer cells attenuates the NF-κB signaling pathway. Jiang et al. reported that in vitro and in vivo tumor growth significantly reduced the induction of metastatic capacity and angiogenesis (Jiang et al. 2016). In non-small cell lung cancer (NSCLC), miR-340 expression was found to be inversely proportional to tumor prognosis. Mimics use of MiR-340

Table 1 Expression levels and functions of miRNAs in different types of cancers

Cancer type	miRNAs	Expression	Putative function	References
Breast cancer	miR-340	Down	Down-regulates the metastatic capability	(Mohammadi-Yeganeh et al. 2016)
	miR-145	Down	Inhibits cell proliferation, migration and invasion	(Kim et al. 2011; Mar-Aguilar et al. 2013; Zheng et al. 2015)
	miR-125b	Down	Suppresses proliferation and invasion	(O'Day and Lal 2010; Mar-Aguilar et al. 2013)
	miR-21	Up	Stimulates cell proliferation and migration, and chemotherapy resistance	(Wang et al. 2011; Yan et al. 2011; Paik et al. 2013; Zhang et al. 2016; Haghnavaz et al. 2018)
	miR-155	Up	Downregulation of FOXO3a and induces chemo-resistance in tumor cell	(Jang et al. 2017; Migita et al. 2017)
	miR-9	Up	Regulates E-cadherin and cancer metastasis	(Ma et al. 2010b; Jang et al. 2017)
Lung cancer	miR-145	Down	Inhibits cell growth and metastasis	(Mataki et al. 2016; Chen et al. 2018a; Li et al. 2018; Skjefstad et al. 2018)
	Let-7 family	Down	Represses cell proliferation and regulates the cell cycle	(An et al. 2015; Castro et al. 2017)
	miR-340	Down	Negative regulator in tumorigenesis and cancer progression	(Fernandez et al. 2014)
	miR-221/222	Up	Stimulates cell proliferation and migration	(Barger and Nana-Sinkam 2015)
	miR-21	Up	Suppresses apoptosis and induces cell growth	(Xie et al. 2010; Yu et al. 2010; Li et al. 2014a; Barger and Nana-Sinkam 2015)
	miR-20a	Up	Promotes cell viability and motility	(Inamura and Ishikawa 2016; Wei and Ran 2018)
	miR-141	Up	Plays role in epithelial-mesenchymal transition (EMT)	(Mei et al. 2014; Barger and Nana-Sinkam 2015)
Prostate cancer	miR-199a	Down	Suppresses proliferation, invasion and chemotherapy resistance	(Qu et al. 2017; Chen et al. 2018b)
	miR-31	Down	Inhibits cell-cycle regulators	(Bhatnagar et al. 2010; Lin et al. 2013; Li and Mahato 2014)
	miR-145	Down	Inhibits invasion, migration and arrests cell cycle	(Sachdeva et al. 2009; Avgeris et al. 2013)
	miR-15a/16-1	Down	Induction of apoptosis, modulate cytokine secretion	(Li and Mahato 2014; Jin et al. 2018; Tao et al. 2018; Zidan et al. 2018)
	miR-148a	Up	Promotes PCa growth	(Dybos et al. 2018)
	miR-221/222	Up	Regulates proliferation, apoptosis, and invasion	(Kneitz et al. 2014; Sun et al. 2014; Wang et al. 2015)
Ovarian cancer	miR-133b	Down	Increases sensitivity to chemotherapy drugs	(Chen et al. 2015; Liu and Li 2015; Yang et al. 2017)
	miR-199a	Down	Regulates drug resistance and enhances cisplatin sensitivity	(Wang et al. 2013; Cui et al. 2018)
	miR-200 family	Up	Potential candidate biomarkers for non-invasive screening	(Sulaiman et al. 2016; Pendlebury et al. 2017)
	miR-141	Up	Plays chemotherapy resistance role	(Mak et al. 2017; Weidle et al. 2018)
	miR-130a/130b	Up	Enhances drug resistance	(Zhang et al. 2013b; Zong et al. 2014; Li et al. 2015)

Table 1 continued

Cancer type	miRNAs	Expression	Putative function	References
Colon cancer	miR-15b	Down	Promotes cellular apoptosis and reverses the chemo-resistance	(González-Vallinas et al. 2014; Zhao et al. 2017)
	miR-200c	Down	Induces cell apoptosis, inhibits invasion, and metastasis	(Chen et al. 2012, 2014a; Pan et al. 2017)
	miR-145	Down	Reverses the development of colon cancer	(Xu et al. 2012; Yu et al. 2015; Li et al. 2016; Qin et al. 2016)
	miR-126	Down	Inhibits colon cancer proliferation and invasion	(Li et al. 2013; Wang 2014; Yuan et al. 2016)
	miR-135	Up	Increases invasion and metastasis	(Valeri et al. 2012)
Bladder cancer	miR-29c	Down	Regulates cell growth and invasion	(Xu et al. 2013a; Fan et al. 2014; Zhao et al. 2015)
	miR-133b	Down	Inhibits cell proliferation, migration and invasion	(Zhou et al. 2013; Chen et al. 2014b)
	miR-96	Up	Promotes cell proliferation and invasion, suppresses apoptosis	(Guo et al. 2012; Wu et al. 2015; Xu et al. 2018)
Osteo-carcinoma	miR-497	Down	Inhibits cell proliferation, migration, and invasion	(Shao et al. 2015; Wang et al. 2016a; Gui et al. 2017)

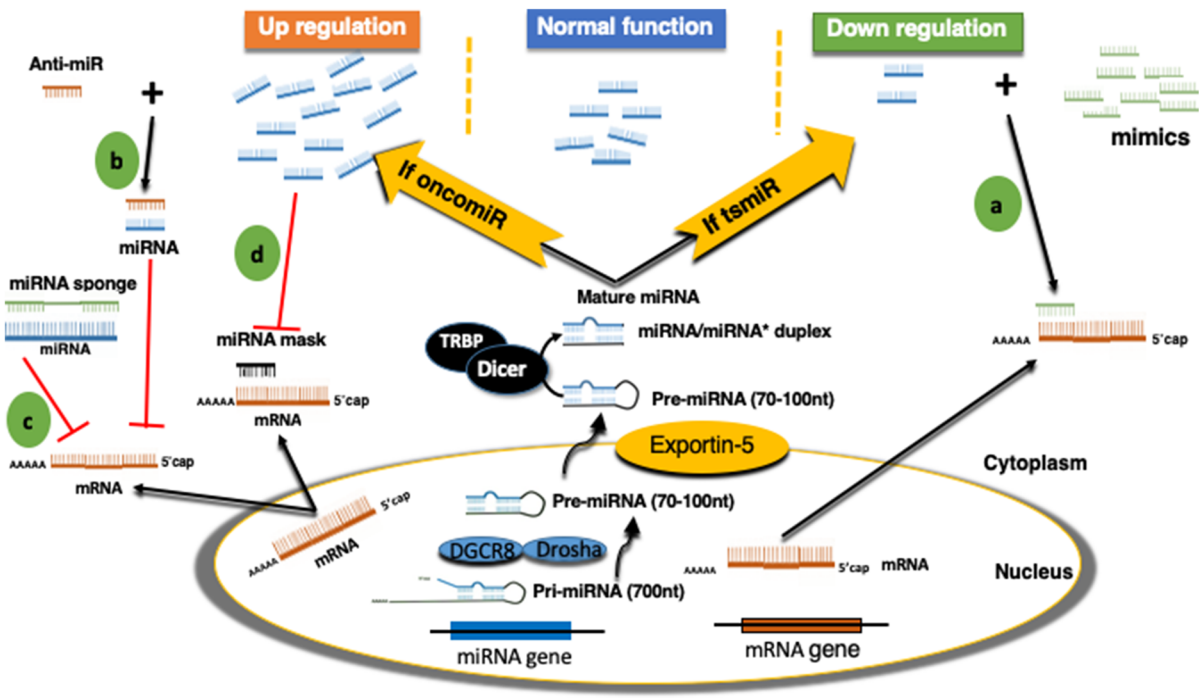

Fig. 1 Schematic diagram of miRNA biogenesis and the therapeutic strategies. miRNA-based molecular cancer therapy for oncogenic (oncomiR) and tumor suppressor miRNAs (tsmiRs). The cancer therapies include miRNA mimics (**a**), anti-miRNA oligonucleotides (anti-miRs) (**b**), miRNA sponges (**c**), and miRNA masking (**d**)

Table 2 Studies involving the use of miRNA mimics and the effects of these mimics on cancer development

Mimic	Cancer type	Effect	References
Let-7 family	Breast	Inhibits growth and migration, and attenuates breast cancer cell metastasis	(Liu et al. 2015; Wang et al. 2016b)
	Gastric	Reverses multidrug resistance	(Yang et al. 2015a)
miR-1	Gastric	Inhibition of cell proliferation, invasion, migration and promotion of apoptosis and cell cycle arrest targeting MET	(Han et al. 2015)
miR-21	Breast	Stimulation of cellular proliferation targeting STAT3	(Yu et al. 2016; Zhang et al. 2016)
	Gastric	Stimulates cancer growth and invasion	(Li et al. 2014b)
	Endometrial	Contributes to cell proliferation	(Qin et al. 2012)
miR-34a	Lung	Inhibits lung tumors in mice targeting Bcl-2	(Trang et al. 2011; Kasinski and Slack 2012)
	Prostate	Inhibits prostate cancer stem cells and metastasis	(Liu et al. 2011)
	Pancreatic	Inhibits pancreatic cancer growth in mice	(Pramanik et al. 2011)
miR-125b	Breast	Targets erythropoietin (EPO) and its receptor (EPOR)	(Ferracin et al. 2013)
	Retinoblastoma	Promotes tumor growth and suppresses apoptosis	(Bai et al. 2016)
miR-143	Gastric	Inhibits cell proliferation and invasion by targeting DNMT3A	(Zhang et al. 2017)
miR-145	Lung	Inhibits migration and invasion by down-regulating FSCN1	(Zhang and Lin 2015)
	Colon	Reduces tumor proliferation and increased apoptosis targeting Pim-1	(Ibrahim et al. 2011)
	Prostate	Modulates tumor sensitivity to radiation and reduces cell growth in the androgen-dependent AR positive cell lines	(Gong et al. 2015; Larne et al. 2015)
miR-148a	Breast	Increases expression of the estrogen receptor-alpha targeting DNMT3A	(Xu et al. 2017)
	Gastric	Enhances cisplatin cytotoxicity	(Li et al. 2017b)
miR-155	Ovarian	Promotes apoptosis	(Chen et al. 2016)
miR-181b/ miR-217	Prostate	Enhances chemo sensitivity of cell	(Lin et al. 2018)
miR-199a	Ovarian	Reverses cisplatin resistance in cells through the inhibition of mTOR targeting HIF1α	(Feng et al. 2017)
miR-203	Cervical	Inhibits the proliferative and migratory capacities of cell	(Yin et al. 2016)
	Endometrial	Decreases SOX4 gene expression and regulates gene expression and physiological processes including proliferation and cell migration	(Huang et al. 2014; Zierau et al. 2018)
	Glioblastoma	Inhibits the proliferation and invasion by directly targeting PLD2	(Chen et al. 2014c)
miR-221/ 222	Prostate	Promotes growth and invasion	(Wang et al. 2015)
	Hepatocellular Carcinoma	Promotes growth and invasion of cell by accompanies activation of NF-kB	(Liu et al. 2016)
miR-340	Lung	Suppresses cell proliferation and induces apoptosis	(Fernandez et al. 2014)
	Hepatocellular Carcinoma	Inhibits the proliferation and invasion targeting JAK1	(Yuan et al. 2017)
	Breast	Inhibits cancer progression	(Shi et al. 2017)
miR-452	Breast	Contributes to the docetaxel resistance and decreases apoptotic rate	(Hu et al. 2014)
miR-544a	Lung	Promotes the invasion of cancer cells	(Mo et al. 2014)
miR-892B	Breast	Activates NF-kB and promotes aggressiveness	(Jiang et al. 2016)

overexpression has been shown to suppress cell proliferation and induce apoptosis in NSCLC cells (Fernandez et al. 2014).

Down-regulation of miR-1 is present in gastric cancer cells. In a study by Han et al., MiR-1 mimic transfusion has been suggested to change this

condition. It has been found that cell proliferation and migration are suppressed by Mimic regulation (Han et al. 2015). Wang and colleagues performed transfection of miR-221/222 mimics in prostate cancer cells. After transfection, it increased cell proliferation activity and inhibited pro-apoptotic effect by suppressing caspase-10 (Wang et al. 2015). The generation of viral vectors (adenoviral, lentiviral and retroviral vectors) that express specific miRNAs can increase the expression of miRNAs in tumor cells (Naidu et al. 2015). Although inhibition of tumor growth of miRNAs synthesized by viral vectors is another approach, miRNA mimics have the potential to be a more promising therapeutic approach since they lack vector-based toxicity.

miRNA antagonists (antagomiRs)

In the literature, it has been shown that miRNAs identified as oncogenes increase in cancer tissues. This leads to increased cell turnover and cell proliferation with increased expression of miRNAs. Inhibition of these miRNAs has become an important area for gene therapy. There are several different methods that are investigated to prevent the binding of oncogene miRNAs to their targets. Inhibiting these miRNAs has been a hope light in cancer therapies to transfect miRNA into cells or tissue to slow down and eliminate tumor growth.

Antagonistic oligonucleotides (antagomiRs, anti-miRs) affect miRNA-related pathways by binding and blocking oncomiR. The single-stranded anti-miRs are based on first-generation antisense oligonucleotides (ASO) designed to target mRNAs or modified by locked nucleic acids (LNAs). These synthetic small RNA molecules have a complementary sequence to inhibit the function of the miRNA by binding strongly (Rupaimoole and Slack 2017). mir-122, which is the first miRNA inhibited by anti-miR contain 3′conjugation cholesterol residues containing 2′-O-methylation of ribose residues (Krützfeldt et al. 2005). They involve the partial modification of phosphodiester bonds via phosphorothioate linkages by replacing one of the bridging oxygen atoms with sulfur (Garofalo and Croce 2013). For example, miR-21, is an oncomiR, known as an anti-apoptotic factor in breast cancer cells, blocks PTEN by activation of the PI3K pathway. Result of MiR-21 up regulation, Bcl2 regulation occurs and apoptosis is inhibited. Anti-miR-21 has been shown to affect breast cancer cells through apoptosis activation and decreased cellular proliferation (Yan et al. 2011). Transfusion of anti-miRNA oligonucleotides targeting MiR-21 has been shown to arrest cell growth in vitro conditions (Chan et al. 2005). Several recent studies on anti-miRNA oligonucleotides in different types of cancer have been shown in Table 3.

miRNA sponges

As an alternative to chemically modified antisense oligonucleotides, Ebert et al., have developed miRNA inhibitors that can be expressed in cells, such as transgenic RNAs. These competitive inhibitors, termed MiRNA sponges, are transcripts exerting from strong promoters containing multiple common binding sites to the target oncomiR (Ebert and Sharp 2010). When the vectors encoding these sponges are transiently transfected into the respective cells, it binds to the target oncomiR and prevents binding to the mRNA (de Melo Maia et al. 2015). Thus, the target mRNA remains free. This mechanism at least releases miRNA targets as well as chemically modified antisense oligonucleotides (Kluiver et al. 2012). Sponges contain two to seven consecutive nucleotides and are linked to the sequences of the respective miRNAs. They specifically inhibit miRNAs with a complementary heptameric sequence so that a single sponge can be used to inhibit members of an entire miRNA family (Ebert et al. 2007). Sponges run by RNA polymerase II (Pol II) contain a fluorescent reporter gene for the identification and classification of processed cells (van Rooij and Kauppinen 2014). In other words, miRNA sponges are composed of transgenic cells and block all other miRNAs of the same family. As indicated in Table 4, miRNA sponges are effectively used in cancers such as breast, lung, renal, melanoma. MiR-9 is an oncomiR that promotes cell migration and metastasis. Downregulation of E-cadherin originating from miR-9 contributes to up-regulation of the gene encoding VEGF (Vascular Endothelial Growth Factor). This is terminated by the activation of beta-catenin signaling. Thus, the tumor causes an increase in angiogenesis. The use of a miRNA sponge in highly malignant cells inhibits miR-9 inhibition and metastasis formation. Ma and colleagues reported using miR-9 sponges that their activity reduced miR-9 activity by 50% (Ma et al. 2010b). Mignacca et al.

Table 3 Studies involving the use of anti-miRNA and the effects of these anti-miRs on cancer development

Anti-miRNA	Cancer type	Effect	References
miR-10b	Breast	Decreases metastasis targeting Hoxd10	(Ma et al. 2010a; Yoo et al. 2015)
miR-21	Breast	Enhances chemo-sensitivity and Inhibition of tumor growth	(Obad et al. 2011; Teng et al. 2013; Giunti et al. 2015)
	Retinoblastoma	Inhibits malignant progression	(Ding et al. 2014)
	Colorectal	Inhibits cell growth and invasive behaviors	(Nedaeinia et al. 2016)
	Hepatocellular	Suppresses cell growth	(Wagenaar et al. 2015)
miR-96	Lung	Exhibits a tumor-suppressor function targeting LMO7	(Wu et al. 2017)
miR-133b	Ovary	Reduces ovarian cancer drug resistance targeting MDR1	(Chen et al. 2015)
miR-155	Breast	Inhibits cancer progression	(Babar et al. 2012)
	Prostate	Promotes chemo-sensitivity and induces cell cycle arrest targeting ANX7	(Cai et al. 2015; Li et al. 2017a)
miR-182	Ovary	Reduces ovarian cancer burden, invasion, and metastasis targeting BRCA1, FOXO3, HMGA2	(Xu et al. 2014)
	Breast	Deceases tumorigenicity of cell	(Chiang et al. 2013)
miR-191	Breast	Increases chemo-sensitivity	(Sharma et al. 2017)
miR-200 family	Endometrioid Carcinoma	Inhibits the growth of cancer cells	(Lee et al. 2011)
	Colon	Decreases proliferation activity and increases apoptosis ability	(Fan et al. 2015)
miR-203	Breast	Suppresses ER-positive breast cancer proliferation and stemness	(Muhammad et al. 2016)
miR-221/222	Hepatocellular Carcinoma	Inhibits growth and invasion	(Park et al. 2011; Liu et al. 2016)
	Breast	Suppresses cell growth and invasion	(Obad et al. 2011)
	Liver tumorigenesis	Inhibits cancer progression	(Pineau et al. 2010)
miR-494	Breast	Inhibition of tumor growth and metastasis	(Liu et al. 2012)

Table 4 Studies involving the use of miRNA sponges and the effects of these sponges on cancer development

Sponges	Cancer type	Effect	References
miR-9	Breast cancer	Inhibits metastasis formation	(Ma et al. 2010b)
miR-10b	Breast cancer	Suppresses the colony formation and inhibits the migration and invasion of the cells	(Liang et al. 2016)
miR-19/miR-155	Hematopoietic cancer	Increases ability of inhibiting cell growth and cell migration	(Mignacca et al. 2016)
miR-21	Hepatocellular carcinoma	Suppresses cell proliferation by up-regulating MAP2K3 expression at both mRNA and protein levels	(Xu et al. 2013b)
	Melanoma	Displays anti-cancer activities	(Liu et al. 2013)
	Non-small cell lung cancer	Reduces proliferation, migration, and invasion of A549 cells by upregulating PDCD4 expression	(Yang et al. 2015b)
	Renal cancer	Inhibited proliferation, migration and invasion of renal cancer cells	(Dey et al. 2012)
miR-221	Melanoma	Displays anti-cancer activities	(Liu et al. 2013)

reported that miRNA sponges used against miR-19 and miR-155 inhibited the function of these miRNAs. This has been shown to increase the induction of p53 and SOCS1 (cytokine signaling-1) in human myeloma cells and mouse leukemia cells. It has been suggested that antagonism of miRNA activity may re-activate cytokine-induced tumor suppressor pathway activity in leukemic cells (Mignacca et al. 2016).

miRNA masking

The miRNA-masking (miR mask) developed by Choi et al., is another strategy based on antisense oligonucleotide technology (Choi et al. 2007). Unlike miRNA sponges, miR-masks completely complement the predicted miRNA binding sites in the 3′-UTR of a specific target mRNA and consist of antisense oligonucleotides modified with single chain 2′-O-methyl (Li et al. 2009). Thus, the miR-mask can prevent the miRNA from accessing the binding site on the target mRNA to disrupt the inhibitory function. By the miR-masking approach, miR-1 and miR-133, which complement the channel coding genes of the pacemaker such as HCN2 and HCN4, are blocked from inhibiting protein expression of these genes. In the miR-mask transfected rat model, heart rate acceleration was possible (Choi et al. 2007). Similar to endogenous miRNA, the effect of AMOs are sequence-specific, not gene-specific. For this reason, AMOs can cause adverse side effects and undesirable toxicity (Xiao et al. 2007). This may be a disadvantage for cancer treatment where multiple pathway targeting may be desirable, although unwanted or non-target factors may be significantly reduced with this approach. The unpredictability, deficiencies and disadvantages of the results of the miRNA masking approach make it far from a promising therapeutic approach. Therefore, there are no consistent studies conducted with this method in recent years.

MiRNA therapeutics in preclinical or clinical trials

Currently, adjuvant chemotherapy and radiation are frequently used in cancer patients except surgical resection. Recent advances provide hope for cancer treatment by regulating gene expression of non-coding RNAs. These developments aim to provide new therapeutic approaches for cancer treatment and to expand a new method to inhibit cancer by miRNA using recently developed LNA technology (Garzon et al. 2010; van Rooij and Kauppinen 2014). Recent innovations in miRNA applications have accelerated new product development. Global miRNA market size is expected to reach 626.27 million USD by 2025 (http://www.businesswire.com). So far, many clinical trials have been initiated using miRNA-based therapeutics. miRNA-based drugs, mainly managed by four RNA therapeutic companies are available. These companies include MiRagen Therapeutics, Regulus Therapeutics, and Mirna Therapeutics.

For example, MRX34, a mimic from miR-34 tumor suppressing liposome formulated lipid carrier NOV40, developed by Mirna Therapeutics, produced complete tumor regression in orthotopic mouse models of liver cancer, no immuno-stimulatory activity, or toxicity in normal tissues. MRX34 is the first miRNA-based therapy in a clinical trial for cancer treatment (Abba et al. 2017). Regulus Therapeutics is generally investigating the use of anti-miRs such as miR-122, miR-10b, miR-221, miR-21, miR-33 in the treatment of diseases such as fibrosis, hepatitis C virus (HCV) infection (Janssen et al. 2013), atherosclerosis and cancer (McLeod et al. 2011; Shah et al. 2016). MiRagen Therapeutics uses chemically modified structures of miRNAs such as miR-15/195, miR-155, miR-29, miR-92 in studies of metabolic and cardiovascular diseases (Querfeld et al. 2016). Finally, SPC3649 (miravirsen) compound, developed by Santaris Pharma, is a miR-122 inhibitor and clinical trials have been performed (Christopher et al. 2016). All these findings showed that miRNAs are now in the category of RNAi-based therapeutics. In particular, for the treatment of personalized cancer, specific miRNA mimic or antagonist sets may be designed for individuals based on miRNA expression profiles. In summary, expression profiling studies provide evidence of the role of miRNAs in cancer diagnosis and prognosis. Together with these new strategies, we hope that miR-1, miR-21, miR-10b, miR-141, miR-145, miR-155, miR-221, miR-340 and miR-494 will be promising candidates.

Conclusion

miRNA-based therapeutic approaches have been devised to provide a high mortality rate in cancer-

related trials. These studies show that the regulation of expression of miRNAs can be controlled through many mechanisms. Given the advantages it has, it is possible that miRNAs can be used to increase the cell sensitivity of cancer drugs and to overcome drug resistance. In order for the method to be applied to be successful, it is very important that it can effectively reach cancerous cells. For this reason, different delivery strategies such as nanoparticle and liposome mediated delivery, especially for miRNA delivery, need to be optimized. miRNA-based therapies must come before some challenges before reaching clinical trials. As with other medicines used in cancer treatment, miRNAs have many molecular targets in both normal and cancer cells. Therefore, the efficiency and reliability of the miRNA needs to be further investigated.

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