Review Article

A narrative review of microRNA therapeutics: understanding the future of microRNA research

Linhui Liang, Xianghuo He

Fudan University Shanghai Cancer Center and Institutes of Biomedical Sciences, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Contributions: (I) Conception and design: X He; (II) Administrative support: X He; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: L Liang; (V) Data analysis and interpretation: L Liang; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Xianghuo He, PhD. Fudan University Shanghai Cancer Center and Institutes of Biomedical Sciences, Shanghai Medical College, Fudan University, 302 Rm., 7# Bldg., 270 Dong An Rd., Shanghai 200032, China. Email: xhhe@fudan.edu.cn.

Objective: In this review, we will discuss miRNA therapeutics in clinical trials and the current challenges of miRNA therapeutics.

Background: MicroRNAs (miRNAs) play crucial roles in the development, proliferation, differentiation, survival and cell metabolism. Many miRNAs are frequently changed in the pathological processes, including cancers. The powerful regulation of miRNAs on the transcriptome enables basic and translational studies of miRNAs on the clinical management of cancer.

Methods: The information used in this narrative review was collected from published literatures and ongoing/completed clinical trials (clinicalTrials.gov).

Conclusions: One advantage of miRNA therapeutic is that one single miRNA can target multiple genes, which makes miRNA a powerful regulator for transcriptome. A great number of studies indicate that miRNAs control the development and progression of cancers. Despite the great success of miRNA therapeutics in pre-clinical studies, a little number of clinical trials are conducted in the present. Currently, the major challenges of miRNA therapeutics are the delivery of miRNA memetic/inhibitor molecules and the immune effects induced by the miRNA drugs. Chemical modification, conjugation of various moieties and package into the nanoparticles can abrogate the adverse effects (AEs) induced miRNA drugs and increase the delivery efficiency. With these approaches, it is promising that miRNA therapeutics may be successfully used in primary cancer therapeutics in the near future.

Keywords: MicroRNA (miRNA) therapeutics; replacement therapy; miRNA inhibitors

Received: 04 July 2021; Accepted: 02 November 2021; Published: 30 December 2021.
doi: 10.21037/pcm-21-28
View this article at: https://dx.doi.org/10.21037/pcm-21-28

Introduction

MicroRNAs (miRNAs) are evolutionarily conserved, small noncoding RNAs consisting of 18–25 nucleotides (nt) that post-transcriptionally regulate gene expression (1). MiRNAs are first transcribed to long primary miRNA (pri-miRNA) transcripts by polymerase II, and then, pri-miRNAs are processed to precursor miRNAs (pre-miRNAs) in the nucleus by the Drosha endonuclease and DGCR (2). Next, the processed pre-miRNAs are exported to the cytoplasm with the aid of exportin 5 and Ran-GTP (2). In the cytoplasm, pre-miRNAs are subsequently processed by the ds-RNase Dicer into mature transcripts (3). Upon maturation, miRNAs are translocated into the RNA-induced silencing complex (RISC), bind the complementary sequences of downstream targets and block the translation of target genes through translational repression or mRNA degradation (4). Compelling evidence indicates that

miRNAs are involved in the initiation and development of cancer (5). It is well established that miRNAs act as tumour suppressor or oncogene in cancers and affect almost every aspect of ten cancer hallmarks, including evading growth suppressor, sustaining proliferative signal, resisting cell death, activating invasion and metastasis, inducing angiogenesis and deregulating cellular energetics, etc. (6). For example, miRNA let-7 represses expression of multiple oncogenes, including *KRAS*, *HMGA2*, *MYC* to regulate the proliferation of cancers and is usually down-regulated in cancers. Dysregulation of let-7 is responsible to evade growth suppressor and sustain proliferative signal of cancers (7). Another miRNA family, the miR-200 family, plays a crucial role in cancer metastasis and angiogenesis by regulating ZEB1 and CXCL1 expression, respectively (8). Moreover, oncogenic transcription factors induce miRNA transcription to participate in the progression of cancers. MYC can induce the transcription of miR-17-92 cluster miRNAs that facilitate proliferation and repress the apoptosis of cancer cells (9). MiRNAs also regulate cancer energetics. MiR-210 is a hypoxia marker miRNA and contributes to the metabolism shift from mitochondrial oxidative phosphorylation to glycolysis through regulating ISCU1 and ISCU2 under hypoxia (10). Furthermore, miRNAs regulate crucial tumour suppressors or oncogenes and are involved in important signalling pathways in cancer progression. Tumour suppressor p53 is a central regulator in cancer suppression. MiRNAs participate into p53 regulation by repressing p53 directly or indirectly (11). MiR-125b, miR-30d and miR-141 directly repress p53 protein through interacting with the 3'-UTR of p53 mRNA. In contrast, other miRNAs, like miR-34a, miR-199a-3p, regulate p53 protein by modulating p53 upstream regulators (11). In addition to p53, tumour suppressor PTEN is also regulated by miRNAs in cancer progression. MiR-21 directly binds to the PTEN mRNA and regulates PTEN expression in cancer cells to promote cancer growth and spreading (12). By controlling crucial proteins in signalling pathway, miRNAs also regulate important signalling pathways in cancer. For example, TGF-β suppresses miR-200 expression in cancer cells. MiR-200 regulates the expression of several components downstream TGF-β signal, like TGF-β itself, TβR-I and Smad2. Thus, TGF-β and miR-200 form a negative feedback circuit and TGF-β represses miR-200 to facilitate TGF-β signalling in cancers (13). As miRNAs play versatile and crucial roles in the initiation and progression of cancer, manipulation of miRNA expression represents a promising way to treat patients with cancer. This review is aimed at discussing miRNA therapeutics in clinical trials and the current challenges of miRNA therapeutics. We present the following article in accordance with the Narrative Review reporting checklist (available at: https://dx.doi.org/10.21037/pcm-21-28).

Methods

The information of this narrative review is collected from published literatures and ongoing/completed clinical trials (clinicalTrials.gov). Only English articles closely relevant to the topic were selected.

Discussion

MiRNA therapeutics in clinical trials: one tiny molecule targets multiple signalling pathways

One advantage of miRNA therapeutics is that one miRNA can target multiple mRNAs, thus regulating multiple signalling pathways, which differs from traditional cancer chemotherapy, in which one drug inhibits one molecule. Currently, more than 2,000 miRNAs have been identified, and approximately 60% of the transcriptome can be regulated by miRNAs. In addition, its short stem loop structure makes a miRNA stable and suitable for signal transduction. The first study linking miRNAs to cancer was conducted in the context of chronic lymphocytic leukaemia (CLL) (14). MiR-15a and miR-16-1, located on chromosome 13q14, were downregulated in 68% of the CLL samples. MiR-15a and miR-16-1 affect many oncogenes including BCL-2, MCL1, CCND1 and WNT3A (15). Moreover, miR-15a and miR-16-1 are deleted in other tumours, such as prostate cancer and glioma (16). Given that the miR-15/16 family affects many important oncogenic targets, miR-15/16 replacement seems to be a potential therapeutic approach to cancer. Malignant pleural mesothelioma (MPM) is resistant to common cancer treatment, and the median survival is approximately 12 months (17). The miR-15/16 family is significantly downregulated in MPM (18). Restoring miR-16 expression in MPM cells profoundly inhibits tumour growth *in vitro* and *in vivo* (18). Therefore, miR-16 mimetics were administered into minicells known as EnGeneIC Dream Vectors (EDVs), also called TargomiRs, and used to treat MPM (19). The first phase 1 in-human clinical trial of TargomiR was performed with MPM patients. EDVs specifically target EGFR, which is expressed in 44–97% of

MPM samples. The results showed that TargomiRs were safe and tolerated by MPM patients. In addition, following TargomiR treatment, 68% (15/22) of the patients had stable disease, and 5% (1/22) showed a partial response, as demonstrated by CT assessment. The results are promising and warrant further investigation of TargomiR combinations with chemotherapy or immunotherapy for MPM treatment.

Another miRNA replacement therapy in clinical trials is the re-expression of miR-34. MiR-34 is a master tumour suppressor miRNA and is transcriptionally regulated by p53 (20). MiR-34 induces apoptosis, cell senescence and cell cycle arrest of tumour cells. The targets of miR-34 are versatile and involved in multiple oncogenic pathways. MiR-34 directly represses targets in the cell cycle (CCND1, CCNE2, and CDK4/6), apoptosis (BCL-2, SIRT1, YY1, etc.), Wnt signalling pathway (WNT1, WNT3, CTNNB1, etc.), MAPK pathway (MAP2K1, RRAS, etc.), cancer cell stemness (MYCN, NANOG, and CD44) and metabolism (ASCL1, LDHA, and IMPDH) (21). The powerful function of miR-34 suggests that miR-34 replacement is a potent therapeutic for cancers. A preclinical animal model also indicated that miR-34 inhibited tumour growth, suppressed metastasis and improved survival *in vivo* (22). MRX34, a miR-34a mimetic encapsulated in liposomal nanoparticles, was applied in a clinical trial in 2014 (23). The trial enrolled adults with different solid tumours who were resistant to the standard treatment. Patients were given MRX34 intravenously daily for 5 days in 3-week cycles. Unfortunately, the trial was closed because four patients died due to serious immune-mediated adverse effects (AEs). This result was unexpected since preclinical animal models suggested that MRX34 was tolerated in all animal models. In addition, the liposome formulation was also tolerated in other therapeutics. Nonetheless, the response rate in this patient cohort was a 4% partial response (3/85 patients). Although the trial was closed, the trial revealed that toxic effects of this kind of drug, including immune-mediated events, which did not appear in preclinical toxicology animal models, should be noticed.

In addition to miRNA replacement, miRNA inhibitors can target oncogenic miRNAs to treat cancers. MiRNA inhibitors are mainly devised based on antisense oligonucleotides. MiR-155 was first identified as an oncogenic miRNA in B cell malignancies and was later reported to be upregulated in other cancers. Importantly, miR-155 transgenic mice developed leukaemia that resembled human high-grade lymphomas or acute lymphoblastic leukaemia (24). MiR-155 is an ideal and promising therapeutic target for cancer treatment, as the target genes of miR-155 in cancers are enriched in multiple oncogenic signalling pathways, including PI3K/AKT, TGF-β and STAT5 (25). Recently, Anastasiadou *et al.* reported that a miR-155 oligonucleotide inhibitor, cobomarsen, slowed the *in vitro* and *in vivo* growth of diffuse large B-cell lymphoma (DLBCL) (26). Cobomarsen is a single stranded oligonucleotide modified by locked nucleic acid (LNA) technology. Cobomarsen can be easily delivered into DLBCL cells without transfection reagent, which facilitates the delivery of cobomarsen *in vivo*. Cobomarsen inhibits proliferation and increases apoptosis of DLBCL cells *in vitro*. Furthermore, intravenous injection of cobomarsen (10 mg/kg) into mice bearing DLBCL xenografts significantly reduced tumour growth *in vivo*. A panel of 12 targets of miR-155 were identified following cobomarsen treatment, and the results showed that cobomarsen can significantly increase the expression of miR-155 targets *in vitro* and *in vivo*. A current cobomarsen clinical trial has enrolled 66 patients suffering cutaneous T-cell lymphoma (CTCL) [mycosis fungoides (MF) subtype] CLL, DLBCL [activated B-cell (ABC) subtype], and adult T-cell leukaemia/lymphoma (ATLL) (https://clinicaltrials.gov/ct2/show/NCT02580552). The results of one patient with DLBCL were reported. This patient was treated with five rounds of chemotherapeutic regimens and relapsed 4 times. The patient was immediately treated with 600 mg intravenous injection of cobomarsen for 5 cycles. The tumour node was significantly reduced following cobomarsen treatment. More importantly, the patient showed no side effects of cobomarsen treatment. Although the patient discontinued cobomarsen treatment due to Progressive Disease (PD) of the disease, the results are still remarkable. Cobomarsen stabilized the disease with few toxic effects. Currently, cobomarsen is also in a phase II clinical trial for the mycosis fungoides CTCL subtype (MF-CTCL) (https://clinical trials.gov/ct2/show/study/NCT03713320). Cobomarsen clinical trials hold promise for miRNA therapy in cancer treatment.

miR-10b was among the most upregulated miRNAs in metastatic breast cancer and was closely correlated with cancer metastasis (27). Overexpressing miR-10b *in vivo* promotes distant metastasis in nonmetastatic breast cancer in a mouse model. Mechanistically, miR-10b regulates multiple metastasis-related genes including HOXD10, KLF4, and NF1 (28). Given these facts, targeting miR-10b provides a new therapeutic strategy for metastatic breast

cancer. Consistent with this, *in vivo* delivery of miR-10b inhibitors significantly blocks breast cancer metastasis (29). An anti-miR-10b nanoparticle drug, TTX-MC138, was developed by Transcode Therapeutics for the treatment of breast cancer, and is currently in the safety and dose escalation phase. Another miR-10b AMO, RGLS5579, is also in the safety and dose escalation phase for glioblastoma treatment.

Challenges of using miRNA therapeutics

One major hurdle of miRNA therapeutics is delivery of miRNA to the correct tumour site *in vivo*. To arrive at tumour sites, miRNA mimetics or inhibitors must be resistant to nuclease degradation in the extracellular space. To resolve this problem, chemical modifications of oligonucleotides are designed to enhance delivery efficiency. Currently, there are ten FDA-approved oligonucleotide drugs, most of which are chemically modified (30). These drugs are mostly delivered locally or to the liver. The nucleic acid backbone, ribose sugar moiety and nucleobase itself can all be chemically modified to enhance delivery using LNAs, 5'-(E)-vinylphosphonate modification and pyrimidine methylation. Cobomarsen is an oligonucleotide with chemical modification (partially LNA, full PS backbone) that does not require an additional delivery system. However, chemical modification of miRNA inhibitors cannot target specific tumour sites *in vivo*. Hence, covalent conjugation of specific moieties to mimetics or inhibitors promotes the uptake of oligonucleotide drugs to specific tissues. The moieties vary, including peptides, antibodies, aptamers and sugars. For example, N-acetylgalactosamine (GalNAc)-conjugated miR-122 was developed to treat hepatitis C virus infection of the liver (Miravirsen, Roche, Switzerland). GalNAc specifically binds to the Asialoglycoprotein receptor on the cell surface of hepatocytes. The interaction between GalNAc and the Asialoglycoprotein receptor leads to the endocytosis of GalNAc-conjugated oligonucleotide drugs (31). Asialoglycoprotein receptor is highly expressed on hepatocytes, so GalNAc-conjugated oligonucleotides can be specifically taken up by hepatocytes. It should be noted that chemical modification might prevent miRNA mimetic recognition and loading into Argonaute and RISC.

In addition to the conjugation of various moieties, miRNA mimetics or inhibitors can also be packaged into nanoparticles to increase uptake efficiency. Advances in nanotechnology and material science present versatile solutions for oligonucleotide drug delivery. The most commonly used nanotechnology for nucleic acid drugs is lipid formulations. MRX34 is a double-stranded miR-34 mimetic in liposome nanoparticles. Pharmacodynamic data indicated that MRX34 suppressed miR-34 targets in the white blood cells of enrolled patients. Whether the target genes in tumours are affected was not evaluated. This indicates that effective delivery of miRNA mimetics to the tumour site remains a challenge for miRNA-based therapeutics. In addition, liposome nanoparticles are relatively large and require large extracellular spaces for entry, and most solid tumours do not have such large spaces.

Another challenge for miRNA therapeutics is the innate immune response induced by miRNA oligonucleotide drugs. Extracellular dangerous signals result in activation of the innate immune response, including exogenous RNAs. Extracellular RNAs are captured by Toll-like receptors (TLRs) on the cell surface, which activate the type I interferon (IFN) response and lead to target cell death (32). Regarding miRNA therapeutics, the immunogenic ability of miRNA mimetics or inhibitors should be specifically reduced to ensure patient safety. MRX34 induced adverse immune effects and resulted in the discontinuation of the clinical trial. However, whether adverse immune effects are induced by MRX34 itself remains undetermined. To abrogate signalling through the TLR family, nucleic acid drugs can be modified using chemical moieties, such as the 2'-O-methyl group, to reduce activation of the immune system.

Perspectives

The development and progression of cancer is a complicated process that involves many genes and signalling pathways. Therefore, miRNA therapy is appealing for cancer therapy since one miRNA can target multiple targets and even many signalling pathways. Decades of studies have provided a large number of preclinical studies involving miRNA mimetics or inhibitors for cancer treatment. However, only a small number of miRNA therapeutics are developed and translated into clinic (*Table 1*). Currently, most clinical trials of miRNAs are evaluating the application of miRNAs in the diagnosis of cancer (https://clinicaltrials.gov/). To date, no miRNA therapeutic has been approved for the clinical treatment of cancer. In 2018, the first RNAi drug, patisiran (Alnylam Pharma), was approved by the FDA to treat hereditary transthyretin amyloidosis (33). This provides hope for the development of other nucleic acid therapeutics, including miRNA therapeutics. Importantly, current

Table 1 MiRNA therapeutics against cancer in clinical trials

miRNA target	Drug name/company	Cancer type	Trial details	Trial identifier
miR-34a replacement	MRX34/Mirna Therapeutics	Primary liver cancer or other selected solid tumours or hematologic malignancies	Multi-centre phase I, terminated	NCT01829971
miR-16 replacement	TargomiR/EnGeneIC	Mesothelioma, non-small cell lung cancer	Multi-centre Phase I, complete	NCT02369198
miR-155 inhibition	Cobomarsen/mirage Therapeutics	Certain lymphomas and leukemias, including CTCL mycosis fungoides subtype, CLL, DLBCL, and ATLL	Multi-centre Phase I, complete	NCT02580552
miR-10b inhibition	RGLS5579/Regulus Therapeutics	Glioblastoma	Safety and dose escalation	Clinical candidate nomination
miR-10b inhibition	TTX-MC138/Transcode Therapeutics	metastatic breast cancer	Safety and dose escalation	Scheduled in 2021–2022

CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; ATLL, adult T-cell leukaemia/lymphoma.

clinical trials of miRNA therapeutics have been applied to cancer patients with resistance to traditional treatment or with untreatable tumours. In addition, the development of next-generation sequencing will help to identify personal molecular profiles of miRNAs in patients and provide miRNA targets for drug development. Untreatable cancers and cancers resistant to traditional treatment will benefit from precision genetic medicine. The promising results of cobomarsen for treating DLBCL and miR-16 TargomiR in MPM treatment suggest that miRNA therapeutics may be used in primary cancer therapeutics in the near future.

Acknowledgments

Funding: This work was supported by grants from National Natural Science Foundation of China (81972253, 81672366).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Zhi-Ming Shao and Xiao-Mao Guo) for the series "Eastern and Western Perspectives on Precision Cancer Medicine" published in *Precision Cancer Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at: https://dx.doi.org/10.21037/pcm-21-28

Peer Review File: Available at: https://dx.doi.org/10.21037/pcm-21-28

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/pcm-21-28). The series "Eastern and Western Perspectives on Precision Cancer Medicine" was commissioned by the editorial office without any funding or sponsorship. Dr. XH serves as an unpaid Associate Editor-in-Chief of *Precision Cancer Medicine* from April 2018 to March 2023 and received grant from National Natural Science Foundation of China, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects for the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281-97.
2. Lund E, Güttinger S, Calado A, et al. Nuclear export of microRNA precursors. Science 2004;303:95-8.
3. Hutvágner G, McLachlan J, Pasquinelli AE, et al. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. Science 2001;293:834-8.
4. Nilsen TW. Mechanisms of microRNA-mediated gene regulation in animal cells. Trends Genet 2007;23:243-9.
5. Iorio MV, Croce CM. MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. EMBO Mol Med 2012;4:143-59.
6. Van Roosbroeck K, Calin GA. Cancer Hallmarks and MicroRNAs: The Therapeutic Connection. Adv Cancer Res 2017;135:119-49.
7. Roush S, Slack FJ. The let-7 family of microRNAs. Trends Cell Biol 2008;18:505-16.
8. Park SM, Gaur AB, Lengyel E, et al. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. Genes Dev 2008;22:894-907.
9. Mogilyansky E, Rigoutsos I. The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. Cell Death Differ 2013;20:1603-14.
10. Dang K, Myers KA. The role of hypoxia-induced miR-210 in cancer progression. Int J Mol Sci 2015;16:6353-72.
11. Liu J, Zhang C, Zhao Y, et al. MicroRNA Control of p53. J Cell Biochem 2017;118:7-14.
12. Meng F, Henson R, Wehbe-Janek H, et al. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology 2007;133:647-58.
13. Suzuki HI. MicroRNA Control of TGF-β Signaling. Int J Mol Sci 2018;19:1901.
14. Calin GA, Dumitru CD, Shimizu M, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A 2002;99:15524-9.
15. Aqeilan RI, Calin GA, Croce CM. miR-15a and miR-16-1 in cancer: discovery, function and future perspectives. Cell Death Differ 2010;17:215-20.
16. Bonci D, Coppola V, Musumeci M, et al. The miR-15a-miR-16-1 cluster controls prostate cancer by targeting multiple oncogenic activities. Nat Med 2008;14:1271-7.
17. Tsao AS, Wistuba I, Roth JA, et al. Malignant pleural mesothelioma. J Clin Oncol 2009;27:2081-90.
18. Reid G, Pel ME, Kirschner MB, et al. Restoring expression of miR-16: a novel approach to therapy for malignant pleural mesothelioma. Ann Oncol 2013;24:3128-35.
19. van Zandwijk N, Pavlakis N, Kao SC, et al. Safety and activity of microRNA-loaded minicells in patients with recurrent malignant pleural mesothelioma: a first-in-man, phase 1, open-label, dose-escalation study. Lancet Oncol 2017;18:1386-96.
20. He L, He X, Lim LP, et al. A microRNA component of the p53 tumour suppressor network. Nature 2007;447:1130-4.
21. Bader AG. miR-34 - a microRNA replacement therapy is headed to the clinic. Front Genet 2012;3:120.
22. Daige CL, Wiggins JF, Priddy L, et al. Systemic delivery of a miR34a mimic as a potential therapeutic for liver cancer. Mol Cancer Ther 2014;13:2352-60.
23. Hong DS, Kang YK, Borad M, et al. Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. Br J Cancer 2020;122:1630-7.
24. Musilova K, Mraz M. MicroRNAs in B-cell lymphomas: how a complex biology gets more complex. Leukemia 2015;29:1004-17.
25. Costinean S, Zanesi N, Pekarsky Y, et al. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. Proc Natl Acad Sci U S A 2006;103:7024-9.
26. Anastasiadou E, Seto AG, Beatty X, et al. Cobomarsen, an Oligonucleotide Inhibitor of miR-155, Slows DLBCL Tumor Cell Growth In Vitro and In Vivo. Clin Cancer Res 2021;27:1139-49.
27. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature 2007;449:682-8.
28. Ma L. Role of miR-10b in breast cancer metastasis. Breast Cancer Res 2010;12:210.
29. Yigit MV, Ghosh SK, Kumar M, et al. Context-dependent differences in miR-10b breast oncogenesis can be targeted for the prevention and arrest of lymph node metastasis. Oncogene 2013;32:1530-8.
30. Herkt M, Thum T. Pharmacokinetics and Proceedings in Clinical Application of Nucleic Acid Therapeutics. Mol Ther 2021;29:521-39.
31. Debacker AJ, Voutila J, Catley M, et al. Delivery of Oligonucleotides to the Liver with GalNAc: From Research to Registered Therapeutic Drug. Mol Ther

2020;28:1759-71.
32. Ablasser A, Poeck H, Anz D, et al. Selection of molecular structure and delivery of RNA oligonucleotides to activate TLR7 versus TLR8 and to induce high amounts of IL-12p70 in primary human monocytes. J Immunol 2009;182:6824-33.
33. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med 2018;379:11-21.

doi: 10.21037/pcm-21-28
Cite this article as: Liang L, He X. A narrative review of microRNA therapeutics: understanding the future of microRNA research. Precis Cancer Med 2021;4:33.