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miR-10b as a Clinical Marker and a Therapeutic Target for Metastatic Breast Cancer

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Abstract

Despite advances in cancer detection and treatment, metastatic breast cancer continues to carry a poor prognosis due to the lack of diagnostic and therapeutic resources that are specific to the metastatic process. MicroRNA-10b (miR-10b) is a small, non-coding RNA that is the focus of many studies due to its unique role as a driver of metastasis. The pathways it is involved in and the properties it confers have been reviewed previously and, collectively, are suggestive of the potential of miR-10b as a clinical marker and as a therapeutic target specific to metastatic disease. With the goal of application of our understanding of miR-10b to the clinic, in this mini-review, we highlight the studies that support the utility of miR-10b for these translational purposes.

Keywords

breast cancer, metastasis, microRNA, biomarker, cancer therapy

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Introduction

MicroRNAs (miRNAs) are small, noncoding RNAs composed of 19–25 nucleotides that function as gene silencers.[1] They have been linked to the regulation of developmental processes since the discovery of the first miRNA in 1993,[2] and their role in pathological processes was demonstrated in 2002, when miR-15 and miR-16–1 were identified as tumor suppressors downregulated in the majority of chronic lymphocytic leukemia cases.[3] Since then, studies have continued to find numerous miRNAs that function as oncogenes or tumor suppressors.

Uniquely, miR-10b was one of the first microRNAs to be implicated specifically in cancer metastasis, with early studies demonstrating that its expression confers properties of increased migration, invasion, and metastatic potential onto breast cancer cells.[4] It has since been associated with other roles in breast cancer models, such as chemoresistance,[5] stemness,[6,7] and viability,[8–10] and its roles appear to be conserved across at least 17 other types of cancer.[11] These studies, as well as mechanistic insights, have been reviewed previously.[11,12] Altogether, these features make miR-10b a potentially valuable clinical marker and promising therapeutic target for the treatment of cancer, particularly metastatic disease, which comprises up to 90% of cancer-related deaths.[13,14] With five-year survival rates for metastatic breast cancer being a dismal 30%,[15] here, we review the utility of miR-10b as a clinical marker for breast cancer and the therapeutic effects observed with its inhibition in *in vivo* breast cancer models using clinically viable methods.

miR-10b as a Clinical Marker in Breast Cancer

In patient primary tumors, miR-10b has been correlated with greater tumor diameter, worse histological and clinical grades, and greater vascularization.[16–18] Additionally, miR-10b appears to positively correlate with HER2 status[16,19] and negatively correlate with both estrogen and progesterone receptors.[16] This variability among breast cancer subtypes, as well as intratumoral

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heterogeneity in miR-10b expression,[20] may explain why studies comparing miR-10b expression in breast primary tumors in general (ie, mixed subtypes and at ratios that vary across studies) versus normal tissues have yielded inconsistent results.[4,16,21,22] Nevertheless, because of the reproducible correlations between miR-10b expression and tumor grade and the phenotypes miR-10b confers in laboratory settings, many studies have begun investigating the potential of miR-10b as a diagnostic or prognostic indicator of breast cancer and metastatic disease. Circulating tumor cells[23] and the secretion of miR-10b by breast cancer cells[24,25] also provide a rationale for serum-based analyses.

Multiple studies suggest that serum miR-10b can be used to discern patients with primary breast cancer from those without,[26,27] with one study reporting a sensitivity of 83.30% and specificity of 100%.[26] This far exceeds the sensitivity of breast cancer markers already in use in the clinic, such as CA15-3 and CEA,[28] and demonstrates the potential of miR-10b as a diagnostic marker. As a prognostic marker, miR-10b expression has been correlated with disease relapse,[22,29] which may be specific to breast cancer, as this correlation was not observed in a pan-cancer meta-analysis.[30] Furthermore, miR-10b expression has been linked to worse overall survival through meta-analysis of three breast cancer studies.[30] MiR-10b may also be useful as a lab value for disease monitoring, as miR-10b expression in patient serum significantly decreased post-operation relative to matched pre-operation levels and further decreased post-radiotherapy.[27] More recently, one group proposed to include miR-10b among a panel of miRNAs for predicting response to treatment,[31] demonstrating another possible clinical application of miR-10b. In support of this, elevated miR-10b in patient serum has been shown to be predictive of anemia in response to chemoradiotherapy.[32]

Given its association with pro-metastatic features, it is possible that miR-10b has the greatest utility as a marker in the context of metastasis. Indeed, one consistent finding is the upregulation of miR-10b in metastatic breast primary tumors relative to non-metastatic tumors or healthy tissue.[4,16–18] Similarly, several studies suggest that miR-10b expression in serum could be used as a marker for breast cancer spread to lymph nodes, finding significant upregulation in patients with metastatic lymph nodes relative to those without.[27,33,34] In one study, the median miR-10b expression of patients with spread to lymph nodes ($n = 35$) was 4.44-fold that of patients without spread to lymph nodes ($n = 25$; $p < 0.01$), and the odds ratio between miR-10b expression and lymph node spread was calculated to be 2.19. When used as a diagnostic test, a threshold expression value identified patients with spread to lymph nodes with a sensitivity of 71% and a specificity of 72%.[33] These findings are particularly notable given that miR-10b is upregulated in lymph node metastasis samples relative to their matched primary tumors, as reported in a study that included 43 pairs of samples across four different types of cancer,[35] as it implicates increased miR-10b at every stage of the metastatic process, from primary tumor to circulation to metastases. These findings also align with the expression patterns of miR-10b relative to HER2, ER, and PR status described earlier, as HER2-overexpressing tumors have increased rates of metastasis relative to hormone receptor-positive tumors.

miR-10b as a Therapeutic Target

The use or inhibition of miRNAs in therapeutic settings has been extensively reviewed in recent publications.[36–38] MiRNAs make for promising therapeutic targets due to their regulation of hundreds of genes that affect several, often-related pathways or processes.[39,40] Given that they are believed to have relatively minor effects on each individual gene,[40] modulation of one miRNA is less likely to perturb normal biological function the way that other therapeutics do. This is evident in studies investigating therapeutic inhibition of miR-10b. Though believed to be an important contributor to early development, genetic knockout of miR-10b in mice is nonlethal, with no significant effect on body weight, overall survival, fertility, or complete blood count.[41] Moreover, the expression of miR-10b in normal tissues is low compared to primary breast tumors.[42] These findings collectively suggest that inhibition of miR-10b in patients would have little or no off-target effects while still potentially having profound effects on cancers that depend on miR-10b activity. Here, we highlight the different approaches that have been used across cancer models to specifically silence miR-10b *in vivo*, their results, and their clinical promise.

At the core of most of the methods used to inhibit miR-10b is the delivery of an anti-miR-10b antisense oligonucleotide (ASO), an RNA molecule with base complementarity to miR-10b. By binding miR-10b, the ASO renders miR-10b nonfunctional and triggers its degradation. The challenges to delivery of ASOs include nucleases, a short blood half-life, and charge-charge repulsion at the cell membrane.[36,37,43] As such, modifications to the ASO or conjugation to a vehicle are generally required. One of the more basic strategies toward therapeutic miR-10b inhibition utilized an ASO with a phosphorothioate backbone, 2′-O-methylation of ribose sugars, and a cholesterol moiety at the 3′ end, all contributing toward stability and delivery.[44] In mice implanted with the spontaneously metastatic 4T1 mouse breast cancer cell line, intravenous administration of the ASO (twice per week, 50 mg ASO/kg bodyweight) resulted in no effect on primary tumor size while decreasing pulmonary metastases by 86%, relative to mice treated with a control oligonucleotide of a similar sequence but with mismatches or with PBS. Important for this study and other methods of therapy using ASOs, this inhibition was shown to be specific to miR-10b and the findings were reproduced when miR-10b was inhibited in the cancer cells prior to implantation, demonstrating that the effects were due to miR-10b suppression in cancer cells and not in other cells (eg, the tumor microenvironment). Moreover, treated mice displayed no behavioral changes, and blood and histologic analyses revealed minimal signs of toxicity.

Although the described modifications to the ASO appear to have overcome some of the limitations to delivery *in vivo*, a major criticism is the high dosage that was required for

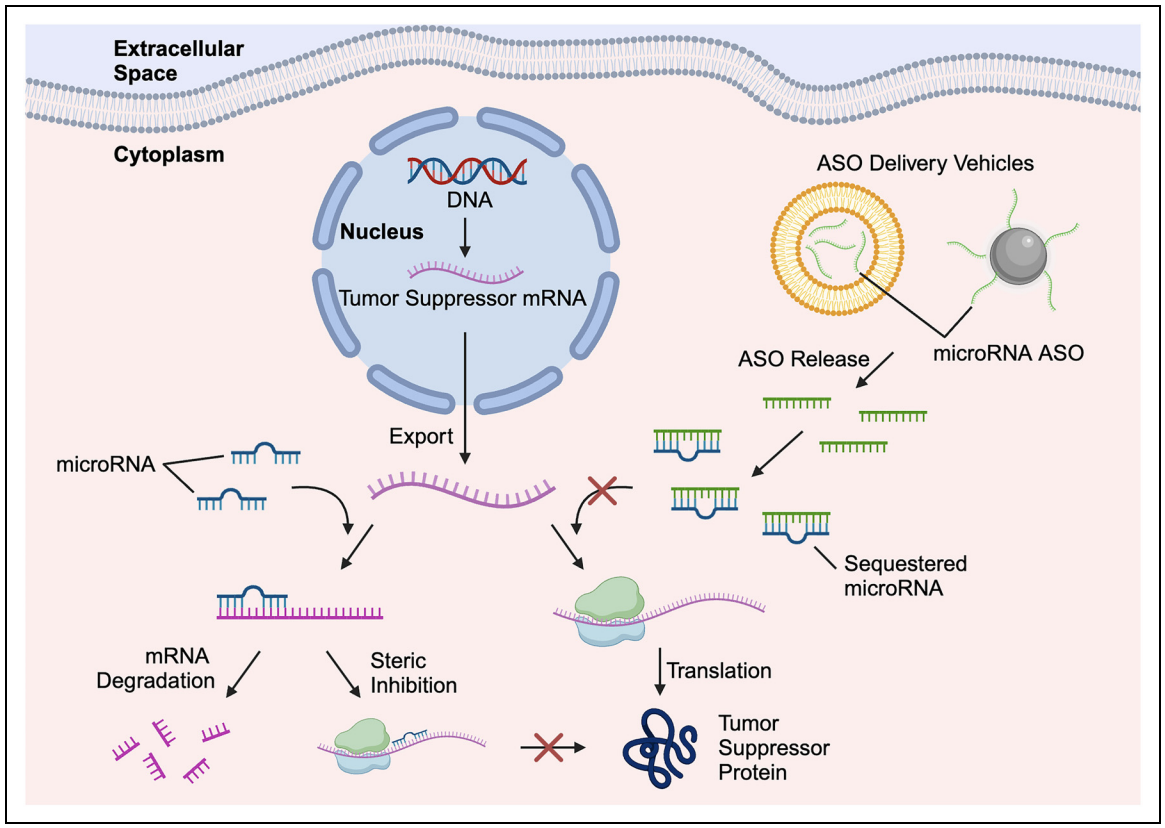

Figure 1. Anti-microRNA Oligonucleotide Delivery. Nanoparticles are at the Forefront of Anti-microRNA Oligonucleotide Delivery. Once Nanoparticles Carrying Anti-microRNA Oligonucleotides Enter the Cell, the Payload is Released from the Nanoparticle Construct, Resulting in Sequestration of Aberrantly Expressed microRNAs. Consequently, Translation of Tumor Suppressor Proteins is Restored, Leading to Reduced Tumorigenesis. Created in BioRender by Kim, B. (2025).

therapeutic effect, which the authors acknowledge may be the reason for liver and spleen enlargement in both the anti-miR-10b and control oligonucleotide treatment mice relative to PBS treatment. To further optimize the use of ASOs as therapeutics, extensive research has gone into the formulation of vehicles for ASO delivery. Various delivery strategies have been employed to increase the delivery efficiency of ASOs to cancers such as conjugation to cell-penetrating peptides, antibodies, and vitamins, such as folate.[45] While these constructs indeed increased the circulation half-life of ASOs and delivery to tumors, one disadvantage of these approaches is the difficulty in tracking accumulation of these constructs in the clinic. At the forefront of delivery methods for miR-10b ASOs are nanoparticles, which have been widely used as vehicles of various payloads, including nucleic acids, to increase delivery to the tumor (Figure 1). Furthermore, nanoparticles are remarkably versatile, allowing them to be engineered for unique and specific properties with precise surface modifications, tailored sizes, and targeting moieties, making them ideal platforms for drug delivery. Due to the modular nature of nanoparticles, a wide variety of pre-clinically and clinically relevant imaging modalities, such as fluorescence imaging and magnetic resonance imaging, respectively, can be conferred by surface modification or nanoparticle core design. In early studies, polylysine nanoparticles carrying anti-miR-10b ASOs demonstrated their ability to inhibit invasion and migration; however these particles were not carried forward into *in vivo* testing.[46]

To date, one of the more promising treatment approaches involves the conjugation of anti-miR-10b ASOs to an iron oxide magnetic nanoparticle (MN) core. This compound, termed MN-anti-miR10b, was first administered intravenously to mice bearing implanted MDA-MB-231 breast cancer cells.[9] Similar to the study using an unconjugated ASO, weekly MN-anti-miR10b (10 mg Fe/kg bodyweight) had no effect on primary tumor size; however, its administration inhibited the formation of lymph node metastases and suppressed the growth of established metastatic tumors, as visualized by bioluminescence imaging (BLI). Histological analyses of lymph node metastases revealed a significant reduction in cell proliferation but not an increase in apoptosis. In a subsequent study, MN-anti-miR10b was used with adjuvant doxorubicin in mice with established spontaneous metastases, and the combination induced stable regression of the metastases by the fourth and final week of treatment.[8] At sacrifice at week 12, there was no evidence of metastasis in the lymph nodes by histology. Importantly, the therapeutic study was initially performed in an immunocompromised model of breast cancer metastases (MDA-MB-231 cells) and was then reproduced in an

immunocompetent model (4T1 cells),[47] and its activity was demonstrated in a case report in a feline model of breast cancer.[48] In all these studies, treatment with MN-anti-miR10b did not appear to cause adverse effects.[8,9,48]

In 2023, MN-anti-miR10b, under the name TTX-MC138 (TransCode Therapeutics), completed an early Phase I clinical trial for its use in "advanced solid tumors",[49] and a multicenter Phase I/II study began in 2024.[50] To date, two cohorts of patients have been administered TTX-MC138 with no reports of significant safety concerns or dose-limiting toxicities.[51] An increased dosage of TTX-MC138 administered to cohort two resulted in greater activity while remaining safe for patients. A third cohort is currently in recruitment for further dosage escalation studies.

Building on the mounting evidence implicating other miRNAs in multiple cancers, especially metastatic breast cancer, recent studies have explored targeting other miRNAs in addition to miR-10b. Devulapally et al investigated the antitumor efficacy of PLGA-b-PEG nanoparticles coloaded with anti-miR-10b and anti-miR-21 (another miRNA implicated in breast cancer) ASOs and decorated with uPA-peptide for tumor cell targeting.[52] These PLGA-b-PEG nanoparticles decreased tumor growth in a subcutaneous, triple-negative breast cancer model after systemic administration. Interestingly, breast cancer cells treated with co-loaded anti-miR-10b and anti-miR-21 PLGA-b-PEG nanoparticles prior to intravenous injection formed tumors significantly slower than untreated cells. In another study, mesoporous silica nanoparticles loaded with anti-miR-10b ASOs and miR-34 mimic was shown to decrease tumor growth in both *ex ovo* and orthotopic *in vivo* models of human triple-negative breast cancer.[53]

An important consideration when using nanoparticles as a delivery vehicle for anti-miR-10b oligonucleotides is the accumulation of these therapeutic nanoparticles in off-target sites. Systemically injected nanoparticles are commonly subject to accumulation in the reticuloendothelial system organs, such as the liver and spleen. Importantly, systemic inhibition of miR-10b does not seem to be associated with adverse effects, as reported by the various studies discussed above.[8,9,41,48] Targeted nanoparticles or biomimetic carriers, such as leukosomes,[54] could improve delivery efficiency of anti-miR-10b oligonucleotides in future studies to improve therapeutic outcomes.

Beyond ASOs, another approach to miR-10b inhibition is the repurposing of existing compounds. One group used a luciferase reporter to screen 450 small molecule inhibitors for miR-10b suppression, identifying thirteen compounds.[55] Of these, the vascular endothelial and platelet derived growth factors inhibitor linifanib was determined to be the only molecule that suppressed miR-10b specifically, finding no effect on five other clinically relevant miRNAs, including miR-10a. Administration of once-daily oral linifanib to mice implanted with bioluminescent MDA-MB-231 breast cancer cells led to tumor bioluminescence, volume, and weight comparable to that of mice treated with liposome-delivered anti-miR-10b ASO, both of which showed decreases in all three parameters relative to vehicle and scrambled ASO controls.[55] As it has already demonstrated therapeutic potential in clinical trials for various cancers, including colorectal,[56] lung,[57] and hematologic,[58] linifanib has unique potential as a readily available miR-10b inhibitor; however, adverse effects may ultimately limit its use.[55] Another non-ASO-based approach toward miR-10b inhibition is the use of anti-miR-10b CRISPR plasmid constructs delivered via lipid-polymer nanoparticles. In this system, payload delivery to the tumor was increased by destruction of the nanoparticle by focused ultrasound.[59] Consistent with other approaches, these nanoparticles failed to reduce primary tumor volume but reduced the number of metastatic lung nodules, further demonstrating the cruciality of miR-10b in breast cancer metastasis development.

While extensively studied in breast cancer, anti-miR-10b nanoparticle therapy has been studied in other cancers including colorectal cancer and glioblastoma. Wang et al investigated the therapeutic efficacy of a novel EGFR-targeted quantum dot nanoparticle to co-deliver the chemotherapy 5-fluorouracil and anti-miR-10b ASO in human colorectal cancer xenografts, resulting in decreased growth of primary tumors and reduced development of metastases in established human cell line xenograft models.[60] Multiple nanoparticle constructs have been developed to target miR-10b in glioblastoma. Teplyuk et al reported on a novel lipid nanoparticle loaded with anti-miR-10b ASOs which was continuously delivered intracranially into the tumor via osmotic pump leading to reduction in orthotopic glioblastoma growth.[61] However, it was insufficient for complete elimination of the tumor. Other groups have explored the co-delivery of anti-miR-10b and anti-miR-21 ASOs as a therapeutic strategy against glioblastoma using an cRGD-targeted PLGA nanoparticle alongside temozolomide (TMZ).[62,63] Chen et al demonstrated the therapeutic potential of MN-anti-miR10b and cytotoxic synergy with TMZ in glioblastoma cell lines *in vitro*,[64] resembling the apparent synergistic effect seen with MN-anti-miR10b and doxorubicin. Interestingly, sequential treatment with MN-anti-miR10b followed by TMZ increased cell killing, suggesting that anti-miR-10b therapy may sensitize cancer cells to chemotherapy. These findings could potentially be translated into the clinic to bolster the effects of traditional chemotherapies and perhaps lower the dose of chemotherapy needed for effective treatment.

Conclusion

In summary, many studies convincingly show that miR-10b overexpression in breast cancer correlates with worse prognosis and disease state. Based on these observations, strong cases have been made that miR-10b is both a robust diagnostic biomarker and specific therapeutic target for metastatic breast cancer. In fact, elevated levels of miR-10b in serum was found to be predictive of worse prognosis in melanoma, non-small cell lung cancer, and pancreatic adenocarcinoma, further supporting the utility of miR-10b as a diagnostic marker.[65–67] Low miR-10b expression in normal tissues, along with the evidence that miR-10b knock-out mice develop normally, indicate that systemic administration of anti-miR-10b therapeutics could be an avenue of precision therapy for metastatic breast cancers.

Moreover, miR-10b has been implicated in the tumorigenesis of many other cancers of metastatic and non-metastatic nature, such as pancreatic cancer, colorectal cancer, and glioblastoma, and has been shown to be effective targets in these cancers. Importantly, in some studies, anti-miR-10b therapy synergized with chemotherapy to improve therapeutic efficacy, suggesting that there is a potential to use it as an adjuvant treatment. Taken together, the critical role of miR-10b in cancer progression in breast cancer as well as other cancers makes it a promising target for novel cancer therapeutics and a potential arm in combination therapy.

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Ethics Statement

N/A for mini-review as we report on other people's findings.

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