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REVIEW

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The potential of microRNAs in cancer diagnostic and therapeutic strategies: a narrative review

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Abstract

Background microRNAs (miRNAs/miRs) are endogenous non-coding RNAs that post-transcriptionally regulate gene expression. Altered miRNA expression promotes oncogenesis by changing the expression of genes involved in key biological pathways in many human cancers. Accumulating evidence reveals that miRNAs have immense potential as diagnostic and prognostic cancer biomarkers based on their capacity to function as oncogenes or tumor suppressors. In addition, translating miRNA-directed therapies from the bench to bedside holds great promise as an innovative therapeutic strategy, contributing to advanced personalized cancer treatment.

Main body This narrative review synthesizes current knowledge on (1) miRNA intracellular and extracellular dynamics enabling gene regulation; (2) technologies for miRNA quantification; (3) validation of miRNA diagnostic/prognostic panels; (4) progress and challenges in developing miRNA-directed cancer therapies, and updates on miRNA clinical trials for cancer monitoring and treatment. Key discoveries and research gaps across these areas are discussed.

Conclusions Cumulative research has established a fundamental understanding of miRNA biology and its correlations with cancer diagnostics and therapy strategies, supporting clinical translational potential. However, complexities within miRNA regulatory networks and methodological inconsistencies necessitate ongoing investigations. Achieving breakthroughs in measurement standardization, biomarker validation, and the development of targeted therapeutic interventions harnessing these post-transcriptional regulators remains crucial for improving cancer diagnosis and treatment.

Keywords MicroRNAs, Cancer, Biomarker, Diagnostic, Therapeutics, Clinical trial

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Background

MicroRNAs (miRNAs/miRs) have rapidly emerged as critical post-transcriptional regulators of gene expression since their initial discovery in the 1990s (Lee et al., 1993; Wightman et al., 1993). Altered miRNA expression promotes oncogenesis by changing the expression of genes involved in key biological pathways across many cancer types (Ali Syeda et al., 2020). Thus, miRNAs have significant potential as minimally invasive biomarkers and therapeutic targets in cancer management. This article provides a narrative review to summarize current knowledge on i) miRNA intracellular and extracellular dynamics enabling gene regulation locally within cells or distally via intercellular transport; ii) technologies for accurate

miRNA quantification; iii) validation of clinically functional miRNA diagnostic/prognostic panels; iv) progress and challenges in developing miRNA-directed cancer therapies, and updates on miRNA clinical trials working to improve cancer monitoring and treatment.

A search of PubMed and Google Scholar using the terms "microRNA", "miR", "cancer", "biomarker", "therapeutics", "clinical trials", and combinations thereof yielded over 15,000 articles published in the past decade elucidating miRNA involvement across malignancies. Key discoveries have cemented miRNAs as critical oncogenic and tumor suppressive pathway regulators (Shenouda & Alahari, 2009; Svoronos et al., 2016; Zhang et al., 2007). Moreover, altered expression of specific miRNA panels consistently correlates with cancer risk, subtype, stage, prognosis, and therapeutic responses (Chan et al., 2011; Luu et al., 2017). However, research gaps remain regarding definitive guidelines for consistent miRNA measurement and target validation. In addition, most miRNA modulators remain stalled in the preclinical phase.

Therefore, this review article aims to synthesize the current advancements and challenges in translating miRNA knowledge into improved clinical cancer management. In addition, we underscored the critical need for standardization of tools and processes to achieve validated miRNA signatures and targeted interventions. Elucidating miRNA functionality in disease while developing innovative therapies promises more precise and personalized strategies to combat cancer.

Main text

Expanding the regulatory world of microRNAs

MicroRNAs constitute a large class of short, non-coding ribonucleic acid (RNA) molecules, approximately 22 nucleotides in length, that post-transcriptionally regulate gene expression (Ha & Kim, 2014). The canonical miRNA pathway involves miRNAs binding to complementary target sites in messenger RNAs (mRNAs) and negatively regulating the expression of those target genes via two mechanisms: repressing mRNA translation and catalyzing mRNA degradation (Chong et al., 2010). Over the past two decades, thousands of evolutionarily conserved miRNAs have been identified across virtually all animal species (Warnefors et al., 2014). Researchers have made remarkable progress in elucidating the diverse regulatory roles of miRNAs across many critical physiological and pathological processes, including cell development, differentiation, proliferation, signaling, apoptosis, metabolism, and immunity (Ardekani & Naeini, 2010). Dysregulation of specific miRNAs has been strongly linked to human diseases such as cancer (Peng & Croce, 2016). Understanding miRNA regulatory networks has not only provided insights into the mechanisms underlying both normal development and cancer pathogenesis, but also revealed exciting opportunities for miRNA-targeted diagnostics, prognostics, and treatment options (Plaisier et al., 2012). As research continues to uncover the extensive influence of miRNAs on the gene regulatory circuitry, miRNAs have solidified their significance as potent post-transcriptional regulators essential for proper cellular functioning (Iacomino, 2023).

To exert control over gene expression, miRNAs must progress through a tightly regulated biogenesis cascade spanning the nuclear and cytoplasmic cellular compartments, as illustrated in Fig. 1. The canonical pathway starts with RNA polymerase II-driven transcription of a long primary miRNA (pri-miRNA) transcript harboring hairpin structures (Ha & Kim, 2014). Within the confines of the nucleus, RNase Drosha, partnered with its cofactor DGCR8, liberates a 60- to 70-nucleotide hairpin intermediary termed the precursor miRNA (pre-miRNA) from the pri-miRNA (Han et al., 2004). Following its export to the cytoplasm via Exportin-5 and the nuclear pore complex, pre-miRNA undergoes additional processing by the cytoplasmic RNase Dicer to yield the mature miRNA duplex (Yi et al., 2003). The unwinding of the duplex by RNA helicases releases the single-stranded, 22-nucleotide mature miRNA loaded into the multi-protein RNA-induced silencing complex (RISC) containing the effector protein Argonaute-2 (Iwakawa & Tomari, 2022). Guidance of RISC to complementary binding sites in the 3' untranslated regions of mRNAs triggers the repression of target gene output (Bartel, 2004). In addition, some intronic miRNAs exploit the splicing of host gene pre-mRNA to bypass the canonical, Drosha/DGCR8-dependent pathway (Lin et al., 2006). In summary, miRNA biogenesis involves coordinated enzymatic processing within nuclear and cytoplasmic compartments to generate mature miRNAs that directly silence gene expression post-transcriptionally.

In addition to their intracellular gene regulatory functions, miRNAs have recently been recognized as mediators of intercellular communication (Arroyo et al., 2011; Hu et al., 2012; Vickers et al., 2011). By secretion into the extracellular environment, miRNAs can traverse to and affect gene expression within recipient cells beyond their cell of origin (Valadi et al., 2007). Most exported miRNAs avoid degradation by extracellular ribonucleases through protective encapsulation, either via packaging into membrane-bound exosomes or complex formation with proteins such as Argonaute-2 (AGO), high-density lipoproteins (HDL) and nucleophosmin-1 (NPM1) (Arroyo et al., 2011; Vickers et al., 2011). Exosomes, which arise from the fusion of multivesicular bodies with the plasma membrane, can fuse with recipient cells to deliver functional miRNA cargos that integrate into endogenous

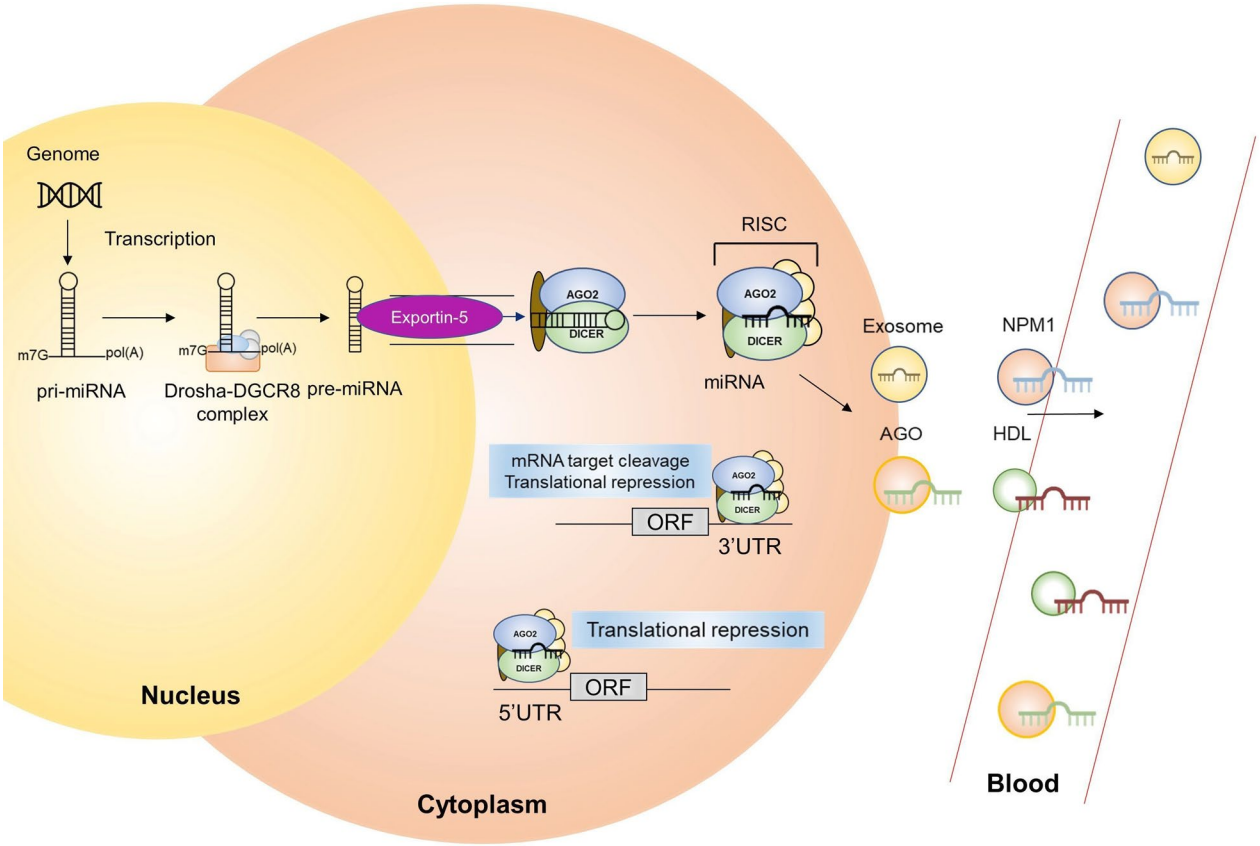

Fig. 1 MicroRNA biogenesis, regulation, and extracellular trafficking

gene-silencing pathways (Théry, 2011; Zhang et al., 2015). Notably, miRNA distribution within secreted exosomes is enriched compared with that in parent cells, implying selective export mechanisms that remain poorly defined (Zhang et al., 2015). Beyond enabling distal gene regulation, recent evidence has revealed that secreted miRNAs may also serve specialized signaling functions—for example, by modulating activation or repression of immune responses (Bauer et al., 2022; Nail et al., 2023). Thus, complex formation and exosomal encapsulation emerge as critical conduits for extracellular miRNA transport involved in cell-to-cell genetic communication and cellular signaling pathways. Elucidating the differential loading and functional roles of secreted miRNAs will reveal a novel dimension of miRNA-mediated control.

Analyzing microRNAs: established and emergent technologies

MicroRNAs undergo stepwise biochemical maturation, resulting in three predominant species—pri-miRNAs, pre-miRNAs, and mature miRNAs. Pri-miRNAs and pre-miRNAs are comparable in size to mRNAs and can be assayed by similar molecular techniques, including real-time quantitative reverse transcription PCR (qRT-PCR) and RNA-sequencing methods (Conrad et al., 2020; Schmittgen et al., 2008). However, due to final Dicer processing that truncates miRNAs to only ~ 22 nucleotides, mature miRNAs present unique detection and analytical challenges owing to their short length. Several approaches have been developed and applied to measure mature miRNA levels directly and indirectly, as depicted in Fig. 2. The emergence of various technologies has enabled increasingly sophisticated interrogation of the expression and functionality of mature miRNAs. However, each method has intrinsic strengths and limitations regarding specificity, accuracy, sensitivity, and scale that warrant consideration when designing miRNA-focused studies, as shown in Table 1.

Northern blotting provides visual confirmation of novel miRNA discovery and benchmarking of miRNA levels because of its ability to separate RNAs by size and specifically probe molecular identity (Koscianska et al., 2011). As depicted (Fig. 2A), it involves electrophoretic separation of denatured RNA samples, transfer to solid membranes, crosslinking, and specific hybridization to radioisotope or chemiluminescent-labeled DNA

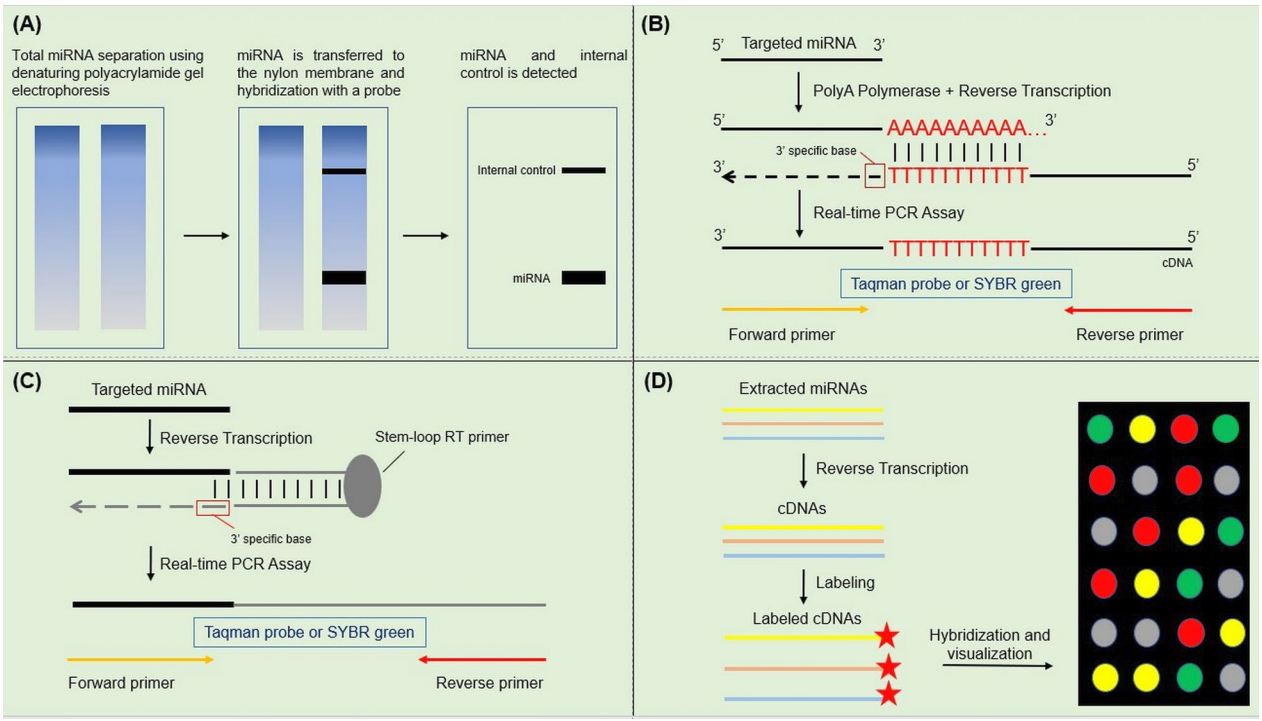

Fig. 2 Popular molecular biology techniques for microRNA detection and quantification. **A** Northern blotting; **B** poly(A) real-time quantitative reverse transcriptase PCR; **C** stem-loop real-time reverse transcriptase PCR; **D** microarray

Table 1 Strengths and weaknesses of different approaches used for miRNA measurement

Methodologies	Strengths	Weaknesses
Northern blotting (Hybridization-based approach)	Could identify the lengths of the targeted miRs Canonical method for validating new miRs High specificity	Demand substantial quantities of RNA Low sensitivity Complicated procedure Could identify only one miR at a time Difficult to quantify
qRT-PCR (Amplification-based detection)	Rapid, high sensitivity and specificity Required a minimal quantity of RNA	The length of the targeted miRs could not be determined Designing primers and probes with precision can be a challenging process Relative quantification Could identify only one miR at a time
Digital PCR (Amplification-based detection)	Rapid, high sensitivity and specificity Required a minimal quantity of RNA Absolute quantification	The length of the targeted miRs could not be determined Designing primers and probes with precision can be a challenging process Chips and reagents are costly Simultaneously detect and quantify specific miR
Microarray (Hybridization-based approach)	Simultaneously detect and quantify a panel of miRs	Demand substantial quantities of RNA Only quantify known miRs Low sensitivity and specificity
Next-generation sequencing (Sequencing-based detection)	Simultaneously detect and quantify a panel of miRs Request an acceptable quantity of RNA High sensitivity and specificity	Complicated procedure The process of library preparation is intricate and can contribute to considerable bias

probes complementary to the miRNA sequence. While regarded as the gold standard, routine use of Northern blotting is constrained by technical demands in probe design, long assay duration, low sensitivity, and high RNA input requirements. Interestingly, the recent inclusion of locked-nucleic acid (LNA) moieties within Northern probes has afforded up to 100-fold enhanced

sensitivity and enabled the detection of low-copy transcripts (Várallyay et al., 2008).

qRT-PCR has supplanted Northern blotting as the foremost tool for rapid, dynamic quantification of individual miRNAs across samples with high sensitivity. The short length of mature miRNAs (~22 nt) necessitates specialized reverse transcription priming and amplification strategies to enable target elongation (Fig. 2B, C). Polyadenylation or stem-loop adapter ligation increases miRNA length for efficient priming (Kramer, 2011; Luo et al., 2012). If miRNA is expressed at a low level, co-purified primary, precursor, and mature miRNA species can impede accurate mature miRNA qRT-PCR, warranting enrichment procedures for low-level miRNAs. However, qRT-PCR provides unsurpassed sensitivity and scalability for targeted miRNA quantification once the assay conditions and data normalization procedures are rigorously validated.

Digital PCR (dPCR) achieves the absolute quantification of miRNAs without external standard curves by applying partition limits to dilute individual molecules into distinct reactions (Cirillo et al., 2020). Two predominant hardware platforms exist—droplet dPCR, which encapsulates reactions in uniform emulsion droplets, and chip-based dPCR, which partitions reactions into thousands of nanoliter wells (Borzi et al., 2017; Cirillo et al., 2020). While the routine assay design mirrors qPCR, the binary positive/negative scoring of reactions enables direct quantification anchored to Poisson statistics. Termed differently across vendors, the approach offers consistent advantages in accuracy and sensitivity over conventional qPCR, as validated through miRNA measurements.

Microarrays offer a powerful capacity to survey the transcriptional states of established miRNA species at reasonable costs for sample throughput (Li & Ruan, 2009). However, signal normalization and baseline subtraction steps are necessary to control for systematic biases and background. Options remain limited for discovering novel miRNAs because the probe content focuses on annotated sequences. However, cost, throughput, and ease-of-use advantages ensure that microarrays remain widely applied, especially for studies validating differentially expressed miRNA biomarkers identified through next-generation sequencing (Ye et al., 2019). Key considerations include selecting appropriate probes and arrays tailored for organism-specific genomes, obtaining sufficient input small RNA, implementing a proper experimental design with biological replication, and applying appropriate computational tools for preprocessing, quality control, and data analyses. If these measures are undertaken, microarrays constitute an efficient platform for miRNA expression profiling. Next, next-generation sequencing (NGS) allows high-throughput analysis from limited samples (Liu et al., 2011). NGS provides discovery and quantification of novel miRNAs with reduced input requirements compared with arrays, albeit at the cost of increased library complexity and inconsistent data from differential preparation methods.

In summary, these global approaches have demonstrated utility in cancer biomarker discovery, but require careful data normalization because standards for miRNA analyses remain provisional. Spiked-in non-human miRNAs provide internal reference controls, although combinations of multiple stably expressed endogenous miRNAs may prove most reliable for cross-study comparisons.

Emergence of the microRNA profile: promises for personalized medicine in diagnosis

Numerous clinical trials are exploring the utility of microRNAs as minimally invasive biomarkers for multiple facets of cancer management, including screening, early detection, and therapy response, as listed in Tables 2 and 3. For instance, completed trials have evaluated miRNA profiles in biospecimens for diagnosing bladder and breast cancer subtypes (NCT03591367 & NCT04516330), although the results remain unpublished. According to ClinicalTrials.gov, ongoing studies continue to assess the diagnostic values of circulating or tissue miRNA signatures across various malignancies such as lymphoma, leukemia, lung, and thyroid cancers (Table 2). Novel approaches even seek to apply miRNA classifiers for cancer screening in stool samples (NCT05346757) or the tumor origin of cancer (miRview® mets). Despite burgeoning studies evaluating miRNAs as clinical biomarkers, addressing standardization in parameters such as specimen handling, processing methodology, and profile normalization remains critical for transitioning classifiers from discovery research into reliable clinical applications. Overall, unraveling miRNA networks through cross-disciplinary and multivariate approaches promises to accelerate translation but requires methodical validation in expanding patient cohorts.

Clinical translation continues to evaluate the predictive utility of miRNA profiles across malignancies. In prostate cancer, two ongoing trials assessed circulating miRNA signatures for forecasting therapeutic responses to androgen deprivation or chemotherapy (NCT04662996 and NCT02366494), whereas others aimed to validate tumor-derived exosomal miRNA panels predicting sensitivity versus resistance to standard regimens (NCT02466113). Across breast, colon, non-small-cell lung, and testicular cancers, additional studies seek to establish miRNA expression-based biomarkers of drug efficacy based

Table 2 Overview of miRNA utilization for cancer screening and diagnosis in clinical trials

miR(s)	Role	Cancer type	Methods	ClinicalTrials.gov Identifier
miR-155	Diagnostic biomarker	Bladder cancer	qRT-PCR	NCT03591367
miR panel	Screening tools	Multicentric breast cancer	Not provided	NCT04516330
5 miR index (endometrial cancer), and miR-200b (ovarian cancer)	Diagnostic biomarkers	Ovarian and endometrial cancer	qRT-PCR and high-throughput sequencing (RNA-seq)	NCT03776630
let-7a and miR-124	Diagnostic biomarkers	Non-Hodgkin's lymphoma and acute leukemia	Real-time PCR	NCT05477667
miR panel	Screening tools	Lung cancer	Custom-made microfluidic card	NCT02247453
Signature of the miRs	Diagnostic biomarkers	Thyroid cancer	NGS	NCT04285476
miR-421, miR-27a-3p	Screening tools	Colorectal cancer	qRT-PCR	NCT05346757
miR-194	Diagnostic biomarker	Prostate cancer	Not provided	NCT04835454
miR panel	Screening tools	42 tumor types	Microarray	miRview® mets (Available)
miR-29, miR-155, miR-138, and miR-204, miR-139, miR-31, miR-375, miR-146, miR-551, miR-221, and miR-22	Screening tools	Thyroid and pancreatic cancer	NGS	ThyraMIR®v2 (Available)

Table 3 Clinical significance of miRNA application in the cancer therapy response

Cancer type	miR(s) studied	Role	Method	Key findings	ClinicalTrials.gov Identifier
Prostate cancer	miR profiles in the blood	Predicting treatment resistance	Not provided	Resistance to metastatic castration-resistant prostate cancer therapy	NCT04662996
Prostate cancer	Exosomal miRs	Predicting the efficacy of androgen deprivation	RNA sequencing	Correlation with the response to androgen deprivation therapy	NCT02366494
Colon cancer (Stage II)	miR-21, miR-20a-5p, miR-103a-3p, miR-106b-5p, miR-143-5p, and miR-215	Characterization of patients undergoing adjuvant chemotherapy	qRT-PCR	Provide information about the adjuvant chemotherapy response	NCT02466113
Non-small-cell lung cancer	Plasma miRs	Evaluate the response to anti-PD-1/PD-L1 treatment	Not provided	Correlation with immunotherapy response	NCT04427475
Triple negative breast cancer	Serum miR profiles	Determine the levels in patients undergoing chemotherapy	Not provided	Correlation with the chemotherapy response	NCT04771871 (Phase 2)
Prostate cancer (low-risk)	miR-141, miR-375	Correlation with focal brachytherapy response	Not provided	Predicting the response to focal brachytherapy	NCT02391051 (Phase 2)

on preclinical implications of specific candidates in treatment pathways (Table 3). Despite the burgeoning clinical investment, methodological variability arising from discrepant specimen procurement, inconsistent platform normalization, and inadequate replication may impede the reproducible development of miRNA biomarker-guided decision algorithms. Achieving standardized operating protocols for miRNA measurement represents a critical prerequisite for the co-development of miRNA-targeted interventions alongside companion diagnostic indicators expected to enable the prospective identification of responsive patient subsets. Underscoring this necessity, the recent approval of patisiran encapsulates the realized potential for clinical miRNA replacement alongside miRNA-based monitoring of tissue drug uptake (Zhang et al., 2020). Ultimately, unraveling the translational applicability of miRNAs in oncology prognosis and prediction relies on a commitment across stakeholders to iterative analytic refinement and transparent reporting during classifier validation in expanded patient cohorts.

Therapeutic targeting of microRNAs: strategies and obstacles

The rapid expansion of knowledge regarding miRNA dysregulation across various cancers has propelled translational efforts to develop miRNA-targeted therapies, principally categorized as either miRNA restoration or inhibition approaches, as delineated in Fig. 3A. Restoration supplements specific miRNAs reduced in disease contexts via the introduction of synthetic miRNA mimics—double-stranded oligonucleotides engineered to replicate the functional guide and passenger strands of the mature miRNA duplex (Wang, 2011a). Effective delivery and stability represent the principal challenges (Segal & Slack, 2020). Unmodified oligonucleotides demonstrate limited stability owing to susceptibility to ribonuclease-mediated degradation and may stimulate innate immune responses (Eberle et al., 2008). Thus, chemical modifications, especially to the 2'-OH ribose position, have been devised to impede nuclease activity while avoiding disruption of miRNA-induced silencing complex function, commonly via 2'-O-methyl or LNA substitutions (Yildirim et al., 2014). Additional phosphorothioate linkage or passenger strand splitting further augments in vivo applicability (Baumann & Winkler, 2014). For sustained functional duration, plasmid or viral vector encoding may maintain intracellular levels, whereas photocaged miRNA conjugates enable spatiotemporal control of activity using light-mediated release.

Alongside restoration strategies, inhibition of overactivated oncomiRNAs or pathomiRNAs represents an alternative therapeutic avenue, achieved via antisense oligonucleotides directly blocking miRNA–mRNA interactions rather than RNase H-mediated cleavage (Christopher et al., 2016). miRNA masks, composed of single-stranded 2'-O-methyl-modified RNAs entirely complementary to miRNA seed sequences, sterically hinder mRNA recognition and RISC loading (Wang, 2011b). Alternatively, high-affinity LNA substitutes ribose with bridged bicyclic monomers to strongly augment miRNA binding while resisting nuclease digestion (Rasmussen & Roberts, 2007). Multivalent miRNA sponges provide a plasmid or viral vector-encoded sink to sequester cytoplasmic miRNAs based on repeated miRNA response elements (Ebert & Sharp, 2010). However, durable overexpression risks system perturbations.

Effective delivery poses additional obstacles to RNA-based gene therapies. Following systemic administration, serum nucleases rapidly degrade unprotected oligos (Baumann & Winkler, 2014). Cationic charge hinders membrane permeability, whereas anionic extracellular matrices impede tissue diffusion (Dominska & Dykxhoorn, 2010; Zámecník et al., 2004). Endosome sequestration further elicits the lysosomal degradation

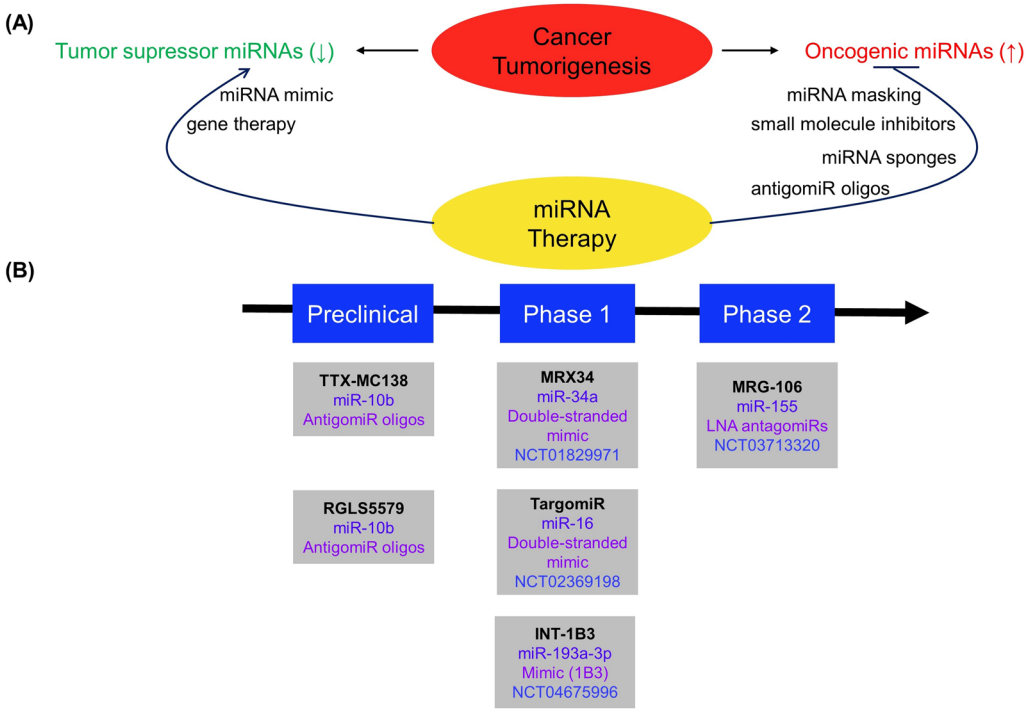

Fig. 3 MicroRNA-based therapy for cancer. **A** miRNA restoration and inhibition therapy; **B** direction of miRNA therapy strategy in cancerous clinical trials

of internalized oligos (Dominska & Dykxhoorn, 2010). These impediments have motivated the development of increasingly sophisticated delivery vectors, including conjugation to lipophilic or targeting moieties (Jeong et al., 2009), viral coat proteins, and multifunctional synthetic or self-assembling nanoparticles capable of overcoming sequential extracellular and intracellular barriers to cargo delivery (Nayerossadat et al., 2012). Combating early instability and inefficient uptake remain principal challenges for the clinical translation of miRNA modulators, although advances in chemical protection and nanotechnology drug carrier design offer promising solutions.

The maturation of RNA interference into clinical reality has sparked burgeoning efforts to translate cancer-associated miRNAs into desperately needed pharmacologic interventions (Naidu et al., 2015). Synthetic miRNA mimics or anti-miRNAs promise precision in redressing pathological imbalances underlying malignancy and other indications. However, early setbacks have illuminated key obstacles impeding systemic delivery and isolating the intended regulatory networks from unpredictable off-target perturbations (Hong et al., 2020). Ongoing campaigns continue to validate foundational miRNA candidates while concomitantly engineering sophisticated new chemical modifications and targeted vectors to fulfill the clinical potential of small RNA medicines, as highlighted in Fig. 3B.

As archetypal examples, miR-34 represents p53-effector miRNAs that elicit tumor suppression and apoptosis through coordinated repression of proliferative networks and untethering of cell death programs (Misso et al., 2014). MiR-34 restoration via a liposomal encapsulated mimic constituted the pioneering clinical foray (MRX34), although immune-mediated toxicity led to trial termination (Hong et al., 2020). Backed by better-tolerated delivery vehicles, replacement approaches continue for other representatives, such as miR-16, which induces apoptosis while inhibiting angiogenesis, proliferation, and invasion/metastasis pathways across models (Reid et al., 2016). Mimic formulations for miR-193a-3p are progressing on the basis of their capacity to reactivate tumor suppressive axes across diverse malignancies (Telford et al., 2021).

Conversely, inhibition of pathologically overexpressed onco-miRNAs such as miR-155 provides an alternative therapeutic approach (Anastasiadou et al., 2021). miR-155 drives hematological and epithelial expansion by usurping immune surveillance and constraining tumor checkpoints (Kalkusova et al., 2022). Although an advanced LNA-anti-miR (MRG-106) reached phase II assessment in T cell lymphoma, business factors cut evaluation short (Seto et al., 2018). In parallel, the blockade of metastasis-promoting miR-10b continues by conjugating anti-miRs to iron oxide nanoparticles (Yoo et al., 2021).

Despite setbacks, diverse miRNA modulators have now undergone molecular refinement en route to specialized delivery vehicles designed to potentiate on-target uptake and clinical translation (Dasgupta & Chatterjee, 2021; Holjencin & Jakymiw, 2022). Harnessing tissue- and genotype-specific miRNA deregulation in an expanding malignancy compendium will bolster the prospects for realizing miRNA medicines.

Discussion and perspectives

This narrative review examined extensive published research implicating miRNAs as critical post-transcriptional regulators with far-reaching impacts across cancer pathogenesis and management. Cumulative evidence has cemented several major roles and findings:

(1): miRNA dysregulation is consistently correlated with oncogenic transformation, tumor phenotypes, disease progression, and therapeutic responses across malignancies. Aberrant miRNA expression profiles reliably distinguish cancerous states, supporting their potential as minimally invasive diagnostic and prognostic biomarkers. However, standardized guidelines remain lacking for consistent biospecimen procurement, processing techniques, quantification platforms, and reference controls in miRNA biomarker development. Moreover, improved cell type- and context-dependent functionality resolution must continue to inform biomarker selection and validation. This provides a deeper insight into the dynamics governing miRNA biogenesis, stability, transport, and target interactions in healthy and cancer settings.

(2): At the mechanistic level, research has elucidated how miRNAs modulate diverse cancer-associated pathways, functioning as both oncogenes and tumor suppressors that exert regulatory control over proliferation, apoptosis, invasion, metastasis, and other hallmark phenotypes. The discovery that differential miRNA expression profiles distinguish pathological states has already facilitated the translation of miRNA signatures as minimally invasive indicators of novel screening approaches, early detection, disease status, and predictors of treatment response.

(3): Correspondingly, engineered miRNA mimics and inhibitors have advanced into clinical development, reflecting the active translation of miRNA-based interventions to therapeutically correct pathological expression imbalances. Significant progress has been made through chemical design innovations that enhance stability and targeted delivery strategies, although overcoming systemic barriers and specificity challenges remain priorities. However, the predictable modulation of the intended miRNA–target networks without unintended impacts remains an ongoing challenge. One principal

obstacle is the activation of innate inflammatory pathways by extracellular RNA sensing mechanisms, which is now being addressed through specialized chemical modifications to improve stability while evading immune detection. In addition, innovative tissue-, cell-, and genotype-specific delivery solutions promise enhanced precision in correcting aberrant miRNA landscapes without globally disrupting systemic equilibrium.

Overall, multidisciplinary research across biochemical, preclinical, and clinical domains persistently advances the fundamental comprehension and clinical translation of miRNA functionalities. Standardization of measurement tools and processes is poised to accelerate the emergence of validated miRNA signatures to improve monitoring and management across indications. In addition, strategic targeting of cancer-linked miRNAs offers prospects for urgently needed pharmacotherapies to harness these small but powerful genetic regulators.

Conclusions

In summary, cumulative research over the past decades has solidified fundamental knowledge regarding miRNA biology and established clinical correlations supporting its translational potential. However, unresolved complexities in miRNA regulatory networks and methodological inconsistencies necessitate continued investigation to enable breakthroughs in measurement standardization, biomarker validation, and targeted therapeutic interventions harnessing these powerful post-transcriptional regulators to improve cancer management.

Abbreviations

miRNA/miR	MicroRNA
RNA	Ribonucleic acid
mRNA	Messenger RNA
pri-miRNA	Primary microRNA
pre-miRNA	Precursor microRNA
RISC	RNA-induced silencing complex
AGO	Argonaute-2
HDL	High-density lipoproteins
NPM1	Nucleophosmin
LNA	Locked nucleic acid
qRT-PCR	Real-time quantitative reverse transcriptase PCR
dPCR	Digital PCR
NGS	Next-generation sequencing

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Author contributions

Writing, review, and editing: M.T.Q. and M.N.N. All authors have read and approved the final network of the manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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