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Review article

Nanoparticle-Mediated Delivery of MicroRNA: A Transformative Approach for Therapeutic Intervention

Abouelhag H. A.*

Microbiology and Immunology Dept., National Research Centre, Dokki, Egypt, 12622.

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Abstract

MicroRNAs (miRNAs) are small, non-coding RNA molecules that play a pivotal role in post-transcriptional gene regulation. Their dysregulation is implicated in a myriad of diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions, making them attractive therapeutic targets or agents. However, the clinical translation of miRNA-based therapies faces significant hurdles, primarily due to poor stability, off-target effects, and inefficient cellular delivery. Nanoparticles (NPs) have emerged as a powerful platform to overcome these barriers. This review comprehensively examines the current landscape of nanocarriers—including lipid-based, polymeric, inorganic, and hybrid nanoparticles—for the safe and effective delivery of miRNA. We discuss the rational design of NPs for enhanced targeting, cellular uptake, and endosomal escape. Furthermore, we highlight recent preclinical and clinical advances in miRNA-nanoparticle therapeutics for oncology, cardiovascular diseases, and other pathologies. Finally, we address the ongoing challenges, biocompatibility concerns, regulatory landscape, and future perspectives in this rapidly evolving field, emphasizing innovations from the last five years.

Keywords:
MicroRNA delivery, nanomedicine, lipid nanoparticles, polymeric nanoparticles, gene therapy, targeted delivery, non-viral vectors, theranostics, clinical translation

I. Introduction

The history of microRNA (miRNA) begins not with a focused search for a new regulatory molecule, but with a puzzling genetic anomaly in the nematode *Caenorhabditis elegans*. In 1993, the laboratories of Victor Ambros and Gary Ruvkun independently characterized the gene lin-4 , which was known to control the timing of larval development. Ambros's group discovered that lin-4 did not encode a protein but produced a small, ~22-nucleotide RNA (Lee, Feinbaum, & Ambros, 1993). Ruvkun's team simultaneously found that this small RNA exhibited imperfect base-pairing to the 3' untranslated region of the lin-14 mRNA to repress its expression (Wightman, Ha, & Ruvkun, 1993). This seminal work revealed a novel, post-transcriptional gene regulatory mechanism. However, lin-4 was considered a curious oddity unique to worms for nearly a decade, and the broader significance of this discovery remained unrealized.

The field underwent a paradigm shift in 2000-2001 with the discovery of a second small temporal RNA, let-7 , also in *C. elegans* (Reinhart et al., 2000). Crucially, let-7 and its regulatory function were found to be highly conserved across bilaterian animals, including humans (Pasquinelli et al., 2000). This conservation suggested the existence of a vast, previously hidden layer of genetic regulation. The subsequent development of cloning and bioinformatics strategies led to an explosion of discoveries, identifying hundreds of similar small RNAs in flies, plants, and mammals (Lagos-Quintana, Rauhut, Lendeckel, & Tuschl, 2001; Lau, Lim, Weinstein, & Bartel, 2001). The term "microRNA" was coined to describe this abundant class of small, endogenous, non-coding regulatory RNAs. It became clear that miRNAs were not mere biological curiosities but fundamental components of the genetic toolkit, involved in fine-tuning nearly every cellular process.

*Corresponding author: *Abouelhag H. A.*
ha.abouelhag@nrc.sci.eg
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The recognition of miRNAs as master regulators of development, cell proliferation, differentiation, and apoptosis inevitably led to the investigation of their role in disease. By the mid-2000s, recurrent patterns of miRNA dysregulation—widespread downregulation, oncogenic amplification, or mutation—were firmly established as hallmarks of human cancers (Calin et al., 2004) and later of cardiovascular, neurological, and metabolic disorders. This established the central therapeutic premise: restoring the function of a lost tumor-suppressor miRNA using synthetic "mimics," or inhibiting an overexpressed oncogenic "oncomiR" with antisense "antagomiRs," could correct pathological gene networks (Rupaimoole & Slack, 2017). However, transforming this premise into a clinical reality immediately confronted the formidable pharmacological challenges of delivering fragile, charged RNA molecules safely and specifically to diseased tissues and cells.

MicroRNAs (miRNAs) are endogenous, single-stranded, non-coding RNAs of approximately 19–25 nucleotides that regulate gene expression by binding to complementary messenger RNA (mRNA) sequences, leading to translational repression or degradation (Bartel, 2018). Consequently, their aberrant expression is a hallmark of numerous diseases. Restoring downregulated miRNAs using miRNA mimics or inhibiting overexpressed miRNAs with anti-miRs (antagomiRs) presents a potent therapeutic strategy.

Despite this promise, the delivery of naked miRNA therapeutics is fundamentally challenged by their rapid degradation by nucleases, renal clearance, poor cellular membrane permeability, and potential immunogenicity (O'Brien et al., 2018). Viral vectors, while efficient, raise safety concerns regarding insertional mutagenesis and immunogenicity. Non-viral nanocarriers offer a compelling alternative, providing protection, enhancing circulation time, enabling passive and active targeting, and facilitating intracellular delivery (Duan & Wang, 2020).

This review synthesizes recent advances (primarily from 2019-2024) in the design, application, and clinical progress of nanoparticle systems for miRNA delivery. It explores the materials science behind nanocarriers, their mechanisms of action, and their transformative potential across various therapeutic domains, with a dedicated, expanded analysis of the critical challenges and future research trajectories.

Main Body

1. Classes of Nanoparticles for miRNA Delivery

1.1. Lipid-Based Nanoparticles (LNPs)

LNPs are the most clinically advanced non-viral delivery systems, notably exemplified by their success in mRNA COVID-19 vaccines. They typically consist of ionizable lipids, phospholipids, cholesterol, and PEG-lipids. The ionizable lipid is crucial for complexation with negatively charged miRNAs and endosomal escape via the proton sponge effect.

Recent innovations focus on novel ionizable lipids with improved biodegradability and reduced toxicity. For instance, Cheng et al. (2021) developed a library of bioreducible lipid nanoparticles for the delivery of miR-34a, demonstrating potent tumor suppression in murine lung cancer models with minimized liver toxicity. Furthermore, **selective organ targeting (SORT)** LNPs, engineered by adding supplementary cationic, anionic, or ionizable lipids, can precisely direct miRNA delivery to extrahepatic tissues like lungs, spleen, or specific immune cells (Cheng et al., 2020).

1.2. Polymeric Nanoparticles

Biodegradable and biocompatible polymers offer tunable properties for miRNA condensation and controlled release. Polyethylenimine (PEI) and chitosan are classical cationic polymers that form polyplexes with miRNA. However, high molecular weight PEI is associated with cytotoxicity. Recent efforts have focused on developing safer derivatives.

For example, low molecular weight PEI grafted with cyclodextrin or polyethylene glycol (PEG) has shown improved safety profiles (Zhou et al., 2022). Similarly, poly(lactic-co-glycolic acid) (PLGA)

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nanoparticles provide sustained release and are FDA-approved for other applications. Conde et al. (2020) designed a PLGA-based nanocarrier co-loaded with anti-miR-155 and a chemotherapeutic drug, achieving synergistic anti-lymphoma effects *in vivo*.

1.3. Inorganic Nanoparticles

Gold nanoparticles (AuNPs), mesoporous silica nanoparticles (MSNs), and magnetic nanoparticles offer unique advantages such as facile surface functionalization, imaging capabilities (theranostics), and stimuli-responsive release.

AuNPs can be conjugated with miRNAs via thiol linkages and their release can be triggered by near-infrared (NIR) light. Wang et al. (2023) developed a gold nanorod system for light-activated release of miR-122, enhancing hepatocellular carcinoma therapy. MSNs, with their high surface area and pore volume, can be loaded with large amounts of miRNA and sealed with stimuli-responsive "gatekeepers" (Li et al., 2021). Superparamagnetic iron oxide nanoparticles (SPIONs) allow for magnetic field-guided delivery and MRI monitoring (Bobo et al., 2020).

1.4. Hybrid and Biomimetic Nanoparticles

Hybrid systems combine materials to synergize their benefits. A common strategy involves a polymeric or inorganic core coated with lipids, enhancing stability and biocompatibility. A groundbreaking trend is the use of **cell-derived biomimetic nanoparticles**, such as exosomes or cell membrane-coated NPs. Exosomes, natural extracellular vesicles, are inherently biocompatible and can cross biological barriers. Alvarez-Erviti et al. (2011) pioneered the use of engineered exosomes for siRNA delivery, a concept now widely applied to miRNA (Jin et al., 2022). Macrophage or cancer cell membrane-coated nanoparticles can leverage natural homing abilities for targeted delivery (Hu et al., 2021).

2. Engineering Nanoparticles for Enhanced Delivery

2.1. Targeting Strategies

Passive Targeting: Relies on the Enhanced Permeability and Retention (EPR) effect, common in tumors with leaky vasculature.

Active Targeting: Achieved by surface functionalization with ligands (e.g., antibodies, peptides, aptamers, small molecules like folate) that bind to receptors overexpressed on target cells. For instance, transferrin receptor-targeted LNPs have been used for brain delivery of miRNA across the blood-brain barrier (Khan et al., 2022).

2.2. Overcoming Intracellular Barriers

Effective delivery requires escape from endosomes. Strategies include the use of ionizable lipids (LNPs), protonatable polymers (e.g., PEI), and fusogenic peptides. Recent work incorporates pH-sensitive linkers or motifs that disrupt the endosomal membrane upon acidification (Zhu & Wang, 2024).

2.3. Stimuli-Responsive Systems

"Smart" NPs release their miRNA cargo in response to specific disease microenvironment cues, such as low pH, elevated reactive oxygen species (ROS), or overexpressed enzymes (e.g., matrix metalloproteinases). This ensures spatiotemporally controlled release, minimizing off-target effects (Wei et al., 2023).

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3. Therapeutic Applications and Recent Advances (2019-2024)

3.1. Oncology

MiRNA replacement (e.g., tumor-suppressive miR-34a, let-7) and inhibition (e.g., oncogenic miR-21, miR-155) are major strategies.

- A lipid-polymer hybrid NP delivering anti-miR-17 showed efficacy in suppressing ovarian cancer progression by derepressing the tumor suppressor PTEN (Zhang et al., 2021).
- A pH-responsive MSN system co-delivering doxorubicin and miR-205 sensitized triple-negative breast cancer cells to chemotherapy (Gan et al., 2022).
- **Clinical Trial:** MRX34, a liposomal miR-34a mimic, entered Phase I trials but was halted due to immune-related adverse effects, underscoring the need for improved carrier design (Hong et al., 2020).

3.2. Cardiovascular Diseases

MiRNAs like miR-92a (anti-angiogenic) and miR-132 (pro-hypertrophic) are key targets.

- PEGylated PEI NPs delivering anti-miR-92a promoted angiogenesis and recovery in a mouse model of myocardial infarction (Hinkel et al., 2019).
- LNPs targeting vascular smooth muscle cells delivered miR-145 to stabilize atherosclerotic plaques in ApoE-/- mice (Zhang et al., 2023).

3.3. Neurological Disorders

Crossing the blood-brain barrier remains a challenge.

- Angiopep-2 peptide-functionalized LNPs successfully delivered miR-124a to glioma cells, inhibiting tumor growth (Wang et al., 2022).
- Exosomes derived from mesenchymal stem cells loaded with miR-29b reduced beta-amyloid plaques in an Alzheimer's disease model (Cui et al., 2021).

4. Expanded Analysis of Challenges and Future Directions

4.1. Multifaceted Challenges in Clinical Translation

4.1.1. Safety and Long-Term Biocompatibility: While acute toxicity profiles are often assessed, the long-term fate of nanomaterials requires deeper investigation. Potential issues include:

- **Accumulation and Chronic Inflammation:** Persistent accumulation of non-degradable or slowly degrading inorganic or polymeric components in organs like the liver and spleen could trigger chronic inflammatory responses or granuloma formation (Bobo et al., 2020).
- **Immunogenicity:** Beyond the payload, the nanoparticle itself can be immunogenic. The generation of **anti-PEG antibodies**, leading to accelerated blood clearance (ABC) and reduced efficacy upon repeated dosing, is a major hurdle (Huang et al., 2024). This has spurred research into alternative stealth coatings like poly(2-oxazoline)s or zwitterionic lipids.
- **Batch-to-Batch Variability:** For complex multicomponent systems like LNPs, minor variations in size, polydispersity, or lipid composition during scale-up can significantly alter biodistribution, efficacy, and toxicity profiles.

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4.1.2. Manufacturing and Scalability: Reproducible, large-scale Good Manufacturing Practice (GMP) production is a non-trivial economic and technical bottleneck.

- **Complexity of Formulation:** Combining miRNAs with nanoparticles often involves multiple steps (e.g., microfluidics mixing, purification, lyophilization), each requiring stringent control.
- **Stability during Storage:** Ensuring long-term stability of the final miRNA-NP complex without aggregation or degradation of the RNA is critical for shelf life and distribution. Lyophilization (freeze-drying) protocols need optimization for each unique formulation.

4.1.3. The Delivery Precision Paradox: While active targeting aims to increase specificity, it introduces new complexities.

- **Target Receptor Heterogeneity:** Target receptor expression can vary between patients, across disease stages, and even within a single tumor, potentially limiting the universality of a targeted approach.
- **The Protein Corona Effect:** Upon intravenous administration, NPs are immediately coated by a dynamic layer of serum proteins, the "protein corona." This corona can mask targeting ligands, redirect NPs to unintended organs (e.g., the mononuclear phagocyte system), and fundamentally alter cellular interactions (Pattipeiluhu et al., 2022). Designing NPs to either exploit or resist corona formation is an active area of research.

4.1.4. Regulatory and Characterization Hurdles: Regulatory agencies like the FDA and EMA face the challenge of evaluating combination products where a biologic (miRNA) is delivered by a complex device (NP).

- **Lack of Standardized Characterization:** Robust and standardized assays to define critical quality attributes (CQAs) such as encapsulation efficiency, *in vivo* release kinetics, and accurate biodistribution beyond fluorescent imaging are needed.
- **Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling:** Developing predictive models for the PK/PD of miRNA-NP complexes is essential for rational dose selection and clinical trial design.

4.2. Future Directions and Innovative Frontiers

4.2.1. Next-Generation Material Discovery and Design: Future efforts will leverage computational and high-throughput tools.

- **AI-Driven Design:** Machine learning and artificial intelligence are being used to screen virtual libraries of millions of lipid and polymer structures to predict key properties like biodegradability, encapsulation efficiency, and *in vivo* performance, accelerating the discovery of novel materials (Xu et al., 2023).
- **Bio-Inspired and Fully Biodegradable Systems:** Inspired by natural biomolecules, researchers are designing peptide-based or nucleic acid nanostructures (e.g., DNA origami) for miRNA delivery, offering exquisite control over size and shape. The push towards fully metabolizable components will enhance safety.

4.2.2. Advanced Targeting and Spatial Control: Moving beyond single-receptor targeting.

- **Dual- and Multi-Targeting Systems:** NPs decorated with two or more different ligands can improve binding affinity and specificity through avidity effects, or target multiple cell populations in a complex disease microenvironment (e.g., both cancer cells and tumor-associated macrophages).
- **Logic-Gated and Exogenous Control:** The future lies in nanoparticles that release their cargo only when multiple disease-specific stimuli are present (AND logic gates), drastically reducing off-target

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effects. Furthermore, the use of exogenous triggers like ultrasound, magnetic fields, or light (as with AuNPs) allows clinicians to spatially and temporally control miRNA release with precision.

4.2.3. Integration with Emerging Therapeutic Modalities: miRNA-NP platforms will not act in isolation.

- **Combinatorial Gene Regulation:** Co-delivery of miRNAs with other regulatory RNAs (siRNA, saRNA) or CRISPR-Cas components for synergistic gene editing and regulation.
- **Immuno-Nanomedicine:** Engineering NPs to not only deliver miRNA but also to actively modulate the immune system—for instance, by incorporating immunostimulatory adjuvants to convert immunologically "cold" tumors into "hot" ones.
- **Gene Circuit Delivery:** Delivering synthetic biology constructs where the delivered miRNA is part of a feedback or amplification circuit within the target cell, creating a sustained therapeutic effect from a single dose.

4.2.4. Personalization and Diagnostics Integration (Theranostics 2.0):

- **Patient-Specific Formulations:** Using diagnostic data (e.g., miRNA expression profiles from a biopsy) to select the optimal miRNA payload. Biomimetic NPs, particularly autologous exosomes or cell membrane coatings, represent a highly personalized delivery vehicle.
- **Quantitative Theranostics:** Developing NPs where the imaging signal (e.g., from a quantum dot or SPION) quantitatively correlates with the miRNA dose delivered and the subsequent therapeutic response, enabling real-time treatment monitoring and adjustment.

4.2.5. Expansion into New Disease Territories: Beyond oncology and cardiovascular disease, future applications will grow in:

- **Regenerative Medicine and Tissue Engineering:** miRNA-NPs to direct stem cell differentiation or promote tissue repair in wounds, bone fractures, or spinal cord injuries.
- **Fibrotic Diseases:** Targeting key miRNAs involved in liver, lung, or kidney fibrosis.
- **Infectious Diseases:** Modulating host miRNA responses to enhance antimicrobial defense or suppress virus replication.

Conclusion

Nanoparticle-based delivery systems have revolutionized the potential of miRNA therapeutics, transforming them from laboratory tools into viable clinical candidates. The path forward, however, is paved with intricate challenges spanning safety, manufacturing, and biological complexity. The next decade will be defined by a shift from empirically designed nanocarriers to intelligently engineered, multifunctional platforms born from computational prediction, deep biological understanding, and advanced fabrication. The convergence of nanotechnology with synthetic biology, AI, and personalized medicine will be crucial. By confronting the outlined challenges with interdisciplinary innovation, miRNA-nanoparticle therapeutics are poised to mature from promising prototypes to mainstream, precision medicines that can fundamentally alter disease trajectories.

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