International Journal of Cell Science & Molecular Biology
ISSN: 2572-1100

Juniper Publishers
key to the Researchers

Review Articles
Volume 8 Issue 3 - November 2026
DOI: 10.19080/IJCSMB.2026.08.555740

Int J cell Sci & mol biol
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MicroRNA-Mediated Gene Regulation in Human Diseases: Mechanisms, Therapeutic Applications, and Challenges

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Submission: October 24, 2026; **Published:** November 20, 2026

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Abstract

MicroRNAs (miRNAs) are small, conserved non-coding RNAs of approximately 22 nucleotides that are central to post-transcriptional gene regulation. Discovered in 1993, miRNAs are transcribed as pri-miRNAs, processed by Drosha and Dicer enzymes, and incorporated into the RNA-induced silencing complex (RISC) to induce translational repression or degradation of target messenger RNAs. A single miRNA can regulate hundreds of genes, thereby controlling vital cellular processes including proliferation, differentiation, apoptosis, development, and stress responses. This review aims to synthesize current knowledge on miRNA biogenesis and mechanisms, examine their dysregulation in major human diseases, and evaluate their emerging therapeutic potential and translational challenges.

Aberrant miRNA expression is a hallmark of numerous diseases. In cancer, miRNAs act as oncogenes (oncomiRs) e.g., miR-21, miR-155, or tumor suppressors e.g., let-7, miR-34a, modulating proliferation, angiogenesis, and metastasis. In cardiovascular diseases, miRNAs such as miR-1, miR-133, miR-208, and miR-21 drive hypertrophy, fibrosis, remodeling, and atherosclerosis. In neurodegenerative disorders including Alzheimer's, Parkinson's, and Huntington's diseases, dysregulated miRNAs contribute to neuroinflammation, protein aggregation, and neuronal death. Therapeutically, miRNA mimics restore suppressor function while antagomirs and locked nucleic acids inhibit pathogenic miRNAs, with several candidates advancing to clinical trials. miRNAs bridge gene regulation and disease pathogenesis with immense therapeutic promise. However, challenges related to delivery efficiency, stability, off-target effects, and immunogenicity limit clinical translation. Advances in nanoparticle delivery, AI-assisted design, and CRISPR-based editing offer viable paths to overcome these barriers and enable personalized miRNA-based therapies.

Keywords: MicroRNAs; Gene Regulation; Cancer; Cardiovascular Disease; Neurological Disorders

Introduction

The discovery of microRNAs (miRNAs) marked a pivotal shift in our understanding of gene regulation. In 1993, the Ambros and Ruvkun groups identified the first microRNA (miRNA), lin-4, in Caenorhabditis elegans [1]. The discovery of the first microRNA (miRNA), lin-4, in 1993 by the Ambros and Ruvkun groups in Caenorhabditis elegans has revolutionized the field of molecular biology [2]. They found that lin-4 was not a protein-coding RNA but a small non-coding RNA that regulates lin-14 at the post-transcriptional level through complementary sequences in the 3′ untranslated region (UTR). They also found that lin-14 was post-transcriptionally downregulated through its 3′ untranslated region (UTR) and that lin-4 had a complementary sequence to that of the 3′ UTR of lin-14. Therefore, they proposed that lin-4 regulates lin-14 at the post-transcriptional level [2].

In 2000, Ruvkun's lab uncovered the highly conserved let-7 microRNA, leading to the subsequent identification of homologous microRNAs across diverse animal species, including humans [3]. This sparked intense cloning and sequencing efforts to identify

microRNAs across the animal kingdom[3]. This resulted in the establishment of miRBase in 2002 as the primary repository for miRNA sequences, annotation, and target prediction [4]. Research growth has been exponential. Since 1993, when the first small non-coding RNA was identified, our knowledge about microRNAs has been exponentially growing [5].

miRNAs are defined as small endogenous non-coding RNAs, typically 21–25 nucleotides in length (~22 nucleotides), that regulate gene expression post-transcriptionally. MicroRNAs (miRNAs) are a class of non-coding RNAs that play important roles in regulating gene expression [6]. The majority of miRNAs are transcribed from DNA sequences into primary miRNAs and processed into precursor miRNAs, and finally mature miRNAs [2]. MicroRNA (miRNA), small molecule in cells, typically about 21–25 nucleotides in length, plays a crucial role in the regulation of gene expression [7]. Key characteristics include their origin from hairpin-structured precursors (pri-miRNA → pre-miRNA → mature miRNA), conservation across species, and ability to target multiple mRNAs via partial complementarity, primarily through a 6–8 nucleotide "seed" region in the 5' end. miRNA biogenesis involves canonical and non-canonical pathways, starting with transcription by RNA polymerase II/III, nuclear processing by Drosha, export via Exportin-5, and cytoplasmic maturation by Dicer [2]. miRNA biogenesis starts with the processing of RNA polymerase II/III transcripts post- or co-transcriptionally. About half of all currently identified miRNAs are intragenic while the remaining are intergenic [2].

Post-transcriptional gene regulation by miRNAs is fundamental because it allows fine-tuned, rapid control of protein levels without altering transcription. miRNAs typically bind the 3′ UTR of target mRNAs, leading to translational repression, deadenylation, and mRNA decay. In most cases, miRNAs interact with the 3′ untranslated region (3′ UTR) of target mRNAs to induce mRNA degradation and translational repression. However, interaction of miRNAs with other regions, including the 5′ UTR, coding sequence, and gene promoters, have also been reported [2]. This mechanism provides robustness, buffering gene expression, and enabling dynamic responses to cellular states. A single miRNA can regulate hundreds of targets, while most protein-coding genes are under miRNA control.

Aberrant miRNA expression is linked to numerous pathologies through mechanisms like acting as oncogenes (oncomiRs) or tumor suppressors [8]. Studies now provide evidence that miRNAs play a pivotal role in a variety of developmental processes and disease [9]. In cancer, miRNAs modulate proliferation, apoptosis, invasion, and metastasis. In cardiovascular disease, they influence hypertrophy, fibrosis, and endothelial function. In neurological disorders, they affect neurogenesis, synaptic plasticity, and neurodegeneration. Gene regulation by microRNAs (miRNAs) plays important roles in development, physiology, and disease. miRNAs are an abundant class of noncoding RNAs [10]. Dysregulation of miRNA expressions or function has been implicated in a variety of diseases, including cancer, cardiovascular disease, neurodegenerative diseases [10]. Therapeutic potential includes miRNA mimics, inhibitors (antagomiRs), and biomarker applications, though challenges like delivery, specificity, and off-target effects remain.

This review provides a broad overview of miRNA-mediated gene regulation mechanisms, with a focus on their emerging roles in cancer, cardiovascular disease, and neurological disorders. It examines therapeutic applications and challenges, highlighting the significance and rapid research growth in this field since its inception over three decades ago. By synthesizing current knowledge, it underscores miRNAs as critical regulators and promising targets for precision medicine. The evolution from an obscure worm gene regulator to a cornerstone of modern molecular biology illustrates the profound impact of miRNA research. Continued advances promise deeper insights into human health and disease.

Biogenesis and Molecular Mechanisms of microRNA-Mediated Gene Regulation

The transcription of a miRNA gene by RNA polymerase II (RNAPII) leads to the production of a primary miRNA transcript (pri-miRNA), which is cleaved in the nucleus by the microprocessor complex, including Drosha and DGCR8, to generate the precursor miRNA (pre-miRNA) [10]. Next, the pre-miRNA hairpin is exported to the cytoplasm by Exportin-5 and processed by Dicer to generate an intermediate miR/miR∗ duplex [10]. Following transcription by RNA polymerase II, Drosha processes the pri-miRNA into a ~60–100 nt hairpin structure termed the pre-miRNA [11]. Through the interaction with Exportin-5 and Ran-GTP, the pre-miRNA is transported into the cytoplasm, where it undergoes a second round of processing catalyzed by Dicer [11]. This cleavage event gives rise to a double-stranded ~22 nt product comprised of the mature miRNA guide strand and the passenger strand [11]. The pre-miRNA hairpin is exported to the cytoplasm by Exportin-5 and further processed by Dicer, resulting in a mature product of 19–24 nucleotide duplex, one strand of which is incorporated into the RNA-induced silencing complex (RISC) [12]. Canonical miRNA biogenesis begins with transcription by RNA polymerase II [13]. Drosha and Dicer are necessary for the biogenesis of most miRNAs [13], and the canonical pathway is Drosha- and Dicer-dependent [14]. In the nucleus, the pri-miRNA is cleaved by the nuclear ribonuclease III enzyme Drosha [15], and Exportin-5 transports the pre-miRNA to the cytoplasm, where Dicer completes maturation [1] (Figure 1).

miRNAs usually interact with the 3′UTR of target mRNAs, leading to mRNA degradation and/or translational repression [16]. They repress gene expression at both the level of mRNA stability, through degradation, and at the level of translation, by inhibiting initiation or degrading polypeptides [16]. miRNAs mediate repression by recruiting the miRNA-induced silencing complex (miRISC), a ribonucleoprotein complex, to target mRNAs

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[17]. Translational repression occurs when miRISC interferes with eIF4E-cap recognition and 40S ribosomal subunit recruitment [17]. For mRNA decay, miRISC interacts with CCR4–NOT and PAN2–PAN3 deadenylase complexes to facilitate poly(A) tail removal [18] (Figure 2).

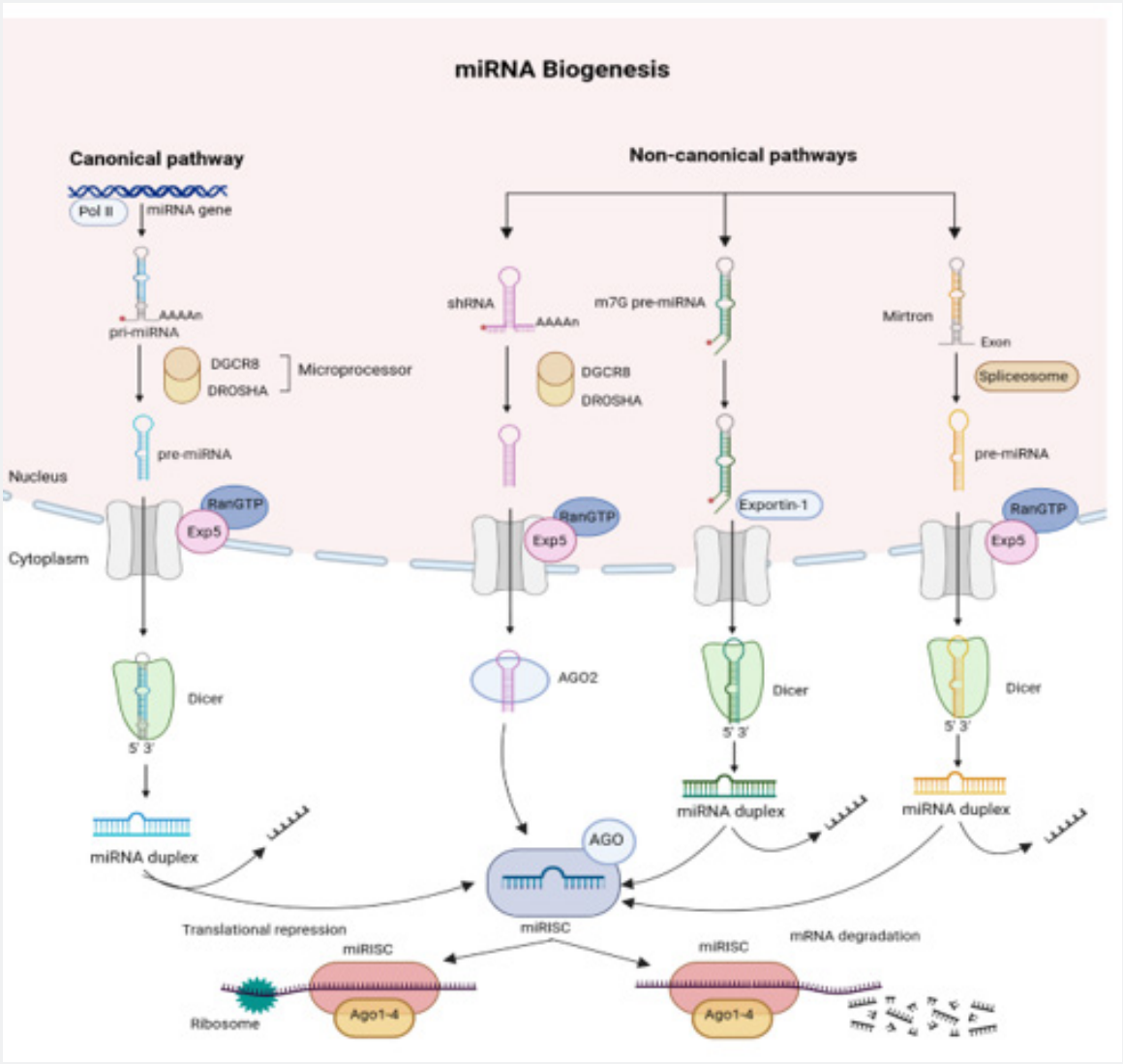

Figure 1: Canonical biogenesis pathway of microRNAs mechanisms of gene regulation by microRNAs.
The canonical pathway in Figure 1 begins with DNA transcription by RNA polymerase II, producing a primary miRNA (pri miRNA) transcript. In the nucleus, the Drosha–DGCR8 complex cleaves this transcript into a precursor miRNA (pre miRNA), a step that defines substrate specificity and prevents premature activity. The pre miRNA is then exported to the cytoplasm by Exportin 5 in association with Ran GTP, ensuring spatial separation between nuclear and cytoplasmic processing. Once in the cytoplasm, Dicer trims the pre miRNA into a ~22 nt duplex, which is subsequently loaded into the RISC complex with Argonaute proteins. One strand is retained as the guide, enabling sequence specific repression or degradation of target mRNAs.
Source: [15]

MicroRNAs are a class of endogenous small noncoding RNAs that regulate complementary mRNAs by inducing translational repression and mRNA decay [18]. Via RISC, miRNAs mediate two modes of silencing: mRNA decay and translational repression [18]. Gene silencing often begins with translational repression followed by deadenylation and decay [18]. The miRISC may also inhibit translation at post-initiation steps by blocking ribosome elongation [19].

The biogenesis of microRNAs relies on a highly coordinated sequence of protein components, where Drosha initiates nuclear processing by cleaving primary miRNA transcripts into precursor miRNAs, a function facilitated by its essential cofactor DGCR8 which ensures accurate substrate recognition (Table 1). The

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resulting pre-miRNAs are then transported from the nucleus to the cytoplasm by Exportin-5 in a Ran-GTP dependent manner, where Dicer mediates cytoplasmic processing to generate mature miRNA duplexes. Finally, Argonaute proteins play a central role in RISC assembly by selecting and loading the guide strand of the miRNA duplex, thereby enabling target mRNA recognition and gene silencing [20-22].

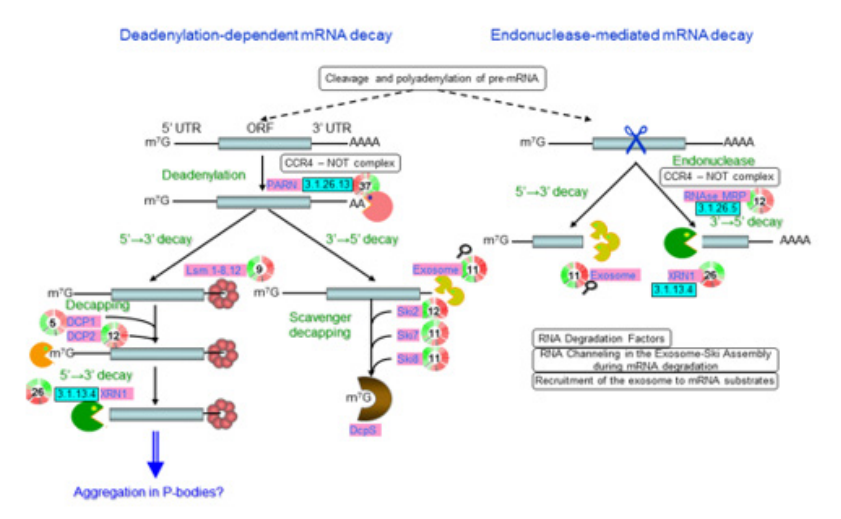

Figure 2: Mechanisms of miRNA-Mediated Gene Regulation.
Figure 2 depicts that microRNAs regulate gene expression by binding to complementary sites within the 3′ UTR of target mRNAs. This binding recruits Argonaute proteins within the RISC complex, which either blocks ribosomal translation or promotes mRNA destabilization and degradation. Through these mechanisms, miRNAs fine tune protein output, buffer stochastic noise in gene expression, and enable rapid cellular adaptation to environmental cues. By preventing aberrant protein accumulation, miRNAs safeguard cellular homeostasis and reduce the risk of pathological states such as cancer or neurodegeneration.
Source: [14]

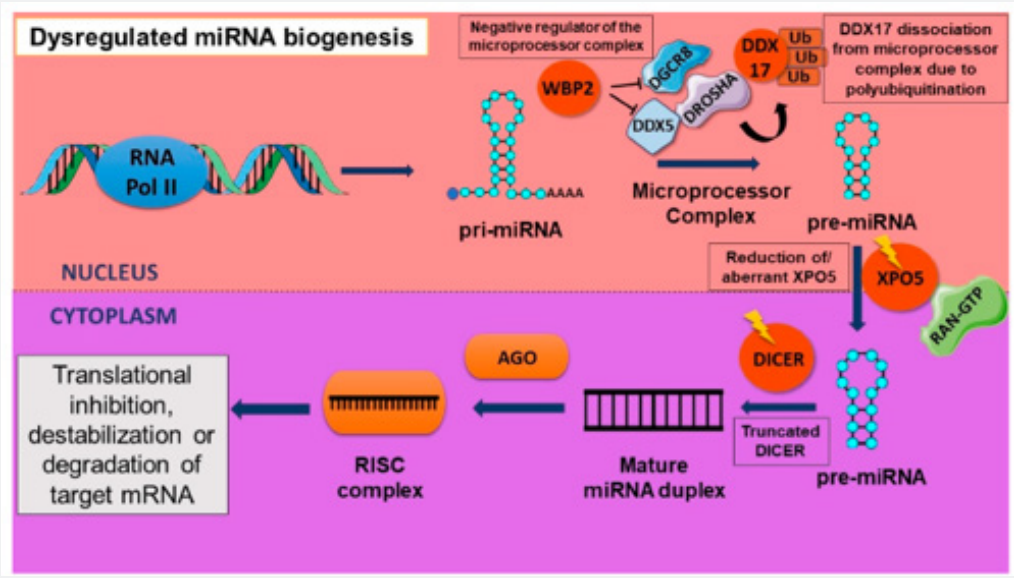

Figure 3: Role of microRNAs in Tumor Development.
MicroRNAs play a dual role in carcinogenesis. Dysregulation of specific miRNAs can lead to oncogene activation, driving uncontrolled cell proliferation and tumor progression. Conversely, loss of tumor suppressive miRNAs results in inactivation of tumor suppressor pathways, facilitating cancer development. Depending on the cellular context, the same miRNA may act as an oncomiR (promoting malignancy) or a tumor suppressor (inhibiting tumor growth). This context dependent activity makes miRNAs powerful modulators of tumor initiation, progression, and metastasis shown in Figure 3.
Source: [13]

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Role of microRNAs in Cancer

Generally, oncogenic miRNAs (oncomiRs) are overexpressed in cancers while tumor-suppressive miRNAs are under expressed [22]. When these oncomiRs or tumor suppressor miRNAs are inhibited or stimulated, respectively, cancer cell proliferation, metastasis, and survival may be reduced [22]. OncomiRs are defined as miRNAs that are overexpressed in tumors, repress tumor-suppressor mRNAs, and stimulate tumor cell proliferation and metastasis [23]. Tumor-suppressor miRNAs (TS-miRNAs) are defined as miRNAs that downregulate cancer progression [23]. miRNAs have therefore been categorized as oncogenes (oncomiRs) or tumor suppressor miRNAs [22]. OncomiRs suppress tumor suppressor genes, promoting cancer cell proliferation and survival, while tumor-suppressor miRNAs inhibit oncogenes, thereby preventing tumor growth [24]. Dysregulation of miRNA expression, whether through overexpression of oncomiRs or downregulation of tumor-suppressive miRNAs, can lead to uncontrolled cell proliferation, evasion of apoptosis, and metastasis [24]. These oncogene miRNAs, called oncomiRs, usually promote tumor development by negatively inhibiting tumor suppressor genes and/or genes that control cell differentiation or apoptosis [25]. Tumor suppressor miRNAs usually prevent tumor development by negatively regulating oncogenes [25]. MiRNAs that promote tumor growth, called oncomiRs, inhibit messenger RNAs of tumor suppressor genes and are therefore overexpressed in cancer. In contrast, TS miRNAs inhibit oncogene messenger RNAs and are therefore under expressed in cancer [26] (Figure 3).

MicroRNAs and Hallmarks of Cancer

miRNAs affect all six hallmarks of malignant cells [25]. In cancer, miRNAs regulate critical processes such as tumor formation, cell proliferation, angiogenesis, invasion, and metastasis by impinging on the expression of key oncogenes and tumor suppressor genes [26]. miR-21 promotes tumorigenesis by enhancing epithelial–mesenchymal transition (EMT), increasing metastatic potential and invasiveness [27] (Figure 4).

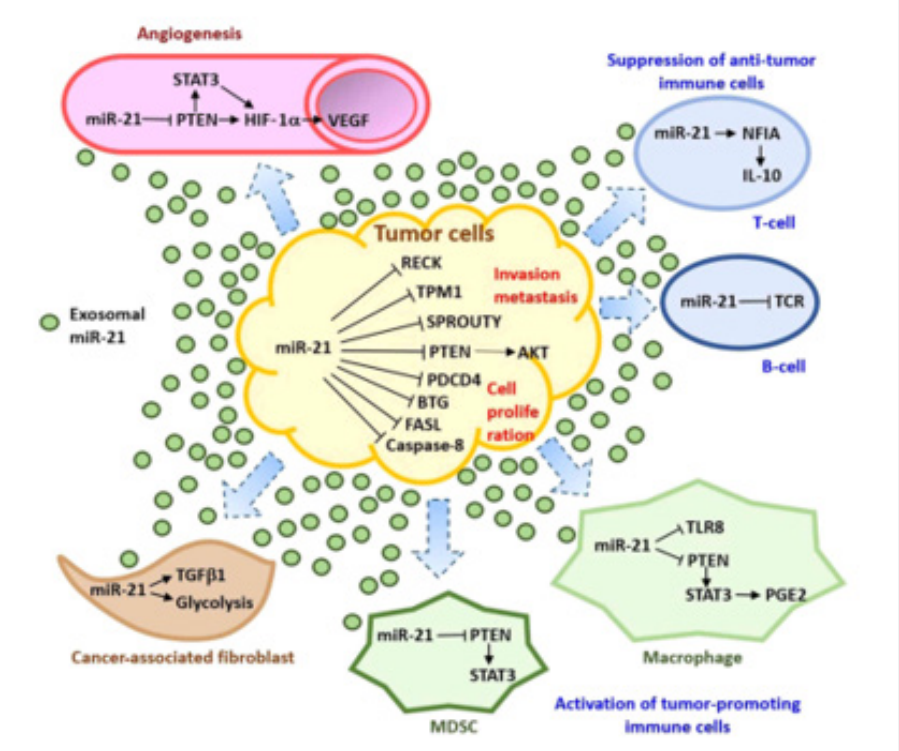

Figure 4: microRNA regulation of cancer hallmarks.
Source: [8]

MicroRNAs orchestrate cancer hallmarks through interconnected regulatory networks [27]. miR-21 is one of the most studied oncomiRs, promoting proliferation and metastasis while suppressing apoptosis [27]. In contrast, miR-34a functions as a tumor suppressor, enhancing apoptosis and cell cycle arrest [28]. miR-155 is frequently dysregulated in hematological malignancies, amplifying oncogenic signaling and immune evasion [29]. The miR-200 family inhibits epithelial to mesenchymal transition (EMT) and angiogenesis, counteracting invasion and metastasis [30].

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Table 1: Key components of the miRNA biogenesis machinery.

Component	Function
Drosha	Nuclear processing
DGCR8	Drosha cofactor
Exportin-5	Nuclear export
Dicer	Cytoplasmic processing
Argonaute	RISC assembly

Source : [9,13]

Table 2: Major cancer-associated microRNAs and their Functions.

miRNA	Target Gene	Cancer Type	Biological Role
miR-21	PDCD4, PTEN, RECK	Multiple (e.g., NSCLC, breast)	Oncogenic – promotes proliferation, invasion, anti-apoptosis
miR-34a	Cyclin D1, CDK4/6	Multiple	Tumor suppressor – inhibits proliferation, induces apoptosis
miR-155	SOCS1, FOXO3A	Breast, lymphoma	Oncogenic – enhances proliferation, metastasis, inflammation
miR-200 family	ZEB1/2	Multiple	Tumor suppressor – inhibits EMT and metastasis

Source: [8]

Table 3: Cardiovascular disease-associated micrornas.

miRNA	Target	Disease Association	Function
miR-1	Hand2, IGF-1	Hypertrophy, HF	Anti-hypertrophic
miR-133	RhoA, CDC42	Cardiac remodeling	Suppresses hypertrophy
miR-21	PTEN, SPRY1	Fibrosis, Atherosclerosis	Pro-fibrotic, pro-inflammatory
miR-208	THRAP1	Hypertrophy, HF	Promotes hypertrophic growth
miR-126	VCAM-1	Atherosclerosis	Endothelial protection

Sources: [18,34]

Table 4: Neurological disease-associated microRNAs

miRNA	Disease	Target Gene	Functional Effect
miR-124	PD, AD	STAT3	Suppresses inflammation
miR-146a	AD, HD	IRAK1	Regulates cytokine production
miR-132	AD, PD	PTBP2	Neuronal protection
miR-155	Multiple	SOCS1	Pro-inflammatory
miR-34a	AD, PD	BCL2	Promotes apoptosis

Source : [18]

Table 5: Current microRNA-based therapeutic approaches

Therapeutic Strategy	Mechanism	Clinical Status
miRNA Mimics	Restore tumor suppressor function	Preclinical / Phase I–II
Antagomirs / Inhibitors	Silence oncogenic miRNAs	Preclinical / Early clinical
miRNA Sponges	Sequester multiple miRNAs	Preclinical
Nanoparticle Delivery	Targeted delivery of mimics/inhibitors	Advancing to trials

Sources: [9,13]

Table 2 below highlights key microRNAs with distinct roles in cancer pathogenesis through specific target genes. miR-21 acts as an oncogenic miRNA by targeting tumor suppressor genes such as PDCD4, PTEN, and RECK in multiple cancers including non-small cell lung cancer and breast cancer, thereby promoting proliferation, invasion and resistance to apoptosis. In contrast, miR-34a functions as a tumor suppressor by repressing cell cycle regulators Cyclin D1 and CDK4/6 across various malignancies,

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inhibiting proliferation and inducing apoptosis. miR-155 exerts oncogenic effects in breast cancer and lymphoma by targeting SOCS1 and FOXO3A, leading to enhanced proliferation, metastasis and inflammatory signaling. Conversely, the miR-200 family serves as a tumor suppressor by targeting ZEB1 and ZEB2, key transcription factors that drive epithelial-mesenchymal transition (EMT), thus inhibiting EMT and metastatic dissemination.

Role of microRNAs in Cardiovascular Diseases

Recent studies have suggested a potentially important role for a family of tiny regulatory RNAs, known as microRNAs (miRNAs or miRs), in the control of diverse aspects of cardiac function in health and disease [28,29]. Although the field of miRNA biology is relatively new, there is emerging evidence that miRNAs may play an important role in the pathogenesis of heart failure through their ability to regulate the expression levels of genes that govern the process of adaptive and maladaptive cardiac remodeling [28]. Changes in the biology of the failing cardiac myocyte include an increase in cell size (hypertrophy) [28]. miR-1 and miR-133 appear to play an important role in the remodeling of the heart that occurs during cardiogenesis, with overexpression of miR-133 resulting in suppression of protein synthesis and inhibition of hypertrophic growth [28-30]. miRNAs therefore play a key role in the pathogenesis of heart failure through their ability to regulate genes that govern adaptive and maladaptive remodeling [31,32]. Recent evidence suggests that miRNAs are differentially expressed in the failing myocardium and play an important role in progression of heart failure [31] (Figure 5).

MicroRNAs in Atherosclerosis and Vascular Dysfunction

Aberrant expression of microRNAs has been implicated in the pathophysiological processes underlying the development of atherosclerosis and cardiovascular disease [31]. miRNAs regulate endothelial gene expression and can regulate endothelial dysfunction and atherosclerosis [32]. Mechano-miRs are responsible for the overall flow-dependent control of endothelial dysfunction and atherosclerosis [32]. The miR-200 family is involved in apoptosis, senescence, inflammation, and endothelial dysfunction associated with atherosclerosis [33]. miR-19a-3p has also been implicated in protecting against endothelial dysfunction in atherosclerosis [34].

Table 3 illustrates the functional significance of specific miRNAs in cardiovascular disease through their target genes. miR-1 exerts anti-hypertrophic effects by targeting Hand2 and IGF-1, and its dysregulation is associated with cardiac hypertrophy and heart failure. Similarly, miR-133 suppresses hypertrophy and cardiac remodeling by targeting RhoA and CDC42, which regulate cytoskeletal and hypertrophic signaling. In contrast, miR-21 promotes adverse outcomes by targeting PTEN and SPRY1, driving fibrosis, atherosclerosis, and pro-inflammatory responses. miR-208 promotes pathological hypertrophic growth and heart failure via repression of THRAP1, a regulator of thyroid hormone signaling. Finally, miR-126 plays a protective role in atherosclerosis by targeting VCAM-1, thereby reducing endothelial inflammation and maintaining vascular integrity [35].

Role of microRNAs in Neurological Disorders

Many miRNAs have been reported and predicted to regulate neurodegeneration in **Parkinson's disease (PD)** [35]. miRNAs have been found to play an important role in PD pathophysiology [36]. Dysregulation of specific miRNAs has been implicated in the modulation of various protein post-translational modifications (PTMs) [36]. In Alzheimer's disease (AD), it has been reported that amyloid-β production involves miRNA-mediated regulation [37]. Dysregulation of miR-7 and miR-34b/c has been associated with PD mitochondrial dysfunction [38-40] (Figure 6).

MicroRNAs are one of the most important regulators mediating microglial activation, polarization, and autophagy, subsequently affecting neuroinflammation [40]. Dysregulation of certain miRNAs can contribute to microglial hyper-activation and persistent neuroinflammation [41,42]. miRNAs influence microglial activation, cytokine production, and phagocytic activity [43]. Activated microglia cause neuroinflammation in two ways: through the production of proinflammatory cytokines and sustained immune activation [42].

Table 4 summarizes the role of selected miRNAs in neurodegenerative diseases through specific targets and functional outcomes. miR-124, implicated in Parkinson's disease (PD) and Alzheimer's disease (AD), suppresses neuroinflammation by targeting STAT3. miR-146a, associated with AD and Huntington's disease (HD), modulates neuroinflammation by regulating cytokine production via IRAK1. miR-132, involved in AD and PD, confers neuronal protection by targeting PTBP2, a regulator of neuronal differentiation and splicing. In contrast, miR-155 exerts pro-inflammatory effects across multiple neurodegenerative conditions by repressing SOCS1, a negative regulator of inflammatory signaling. Lastly, miR-34a, linked to AD and PD, promotes neuronal apoptosis through inhibition of the anti-apoptotic gene BCL2, contributing to neurodegeneration

Therapeutic Applications of microRNAs

microRNA Mimics and Inhibitors

The development of miRNA mimics and inhibitors has brought new hope for cancer treatment, especially in reversing cancer drug resistance [40]. miRNA mimics are synthetic double-stranded molecules with limited chemical modifications that closely resemble naturally present microRNAs [41]. Both miRNA mimics and inhibitors are important tools in functional genomics and gene regulation research, enabling modulation of miRNA activity [42]. Preclinical studies have extensively validated their therapeutic potential in various cancer models [43]. Results suggest that mimics based on the consensus sequence of the miR-15/107 group have therapeutic potential across multiple cancer types [41] (Figure 7).

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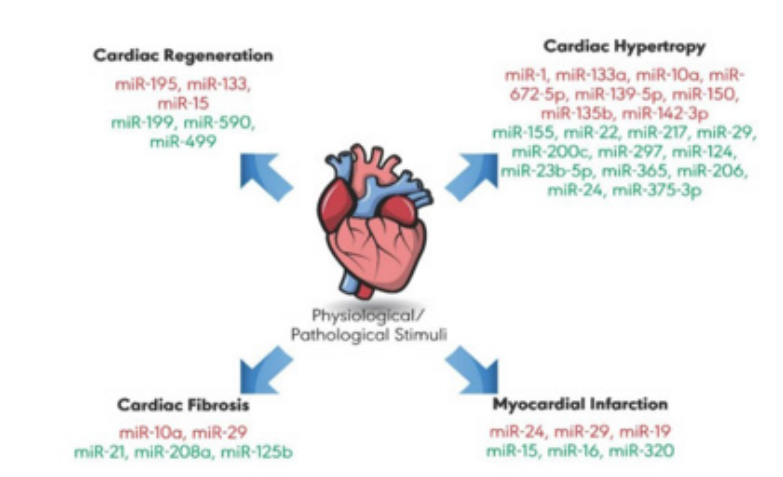

Figure 5: microRNA signaling pathways in cardiovascular disease.
Figure 5 MicroRNAs are central regulators of cardiovascular signaling. miR 1 targets transcription factors like Hand2, influencing cardiac conduction and hypertrophic signaling. miR 133 suppresses hypertrophy by modulating RhoA and Cdc42, but its downregulation promotes pathological growth. miR 21 enhances fibrotic responses through inhibition of PTEN and activation of MAPK pathways, driving maladaptive remodeling. miR 208 regulates myosin gene expression and contributes to hypertrophy and heart failure when dysregulated.
Source: [9]

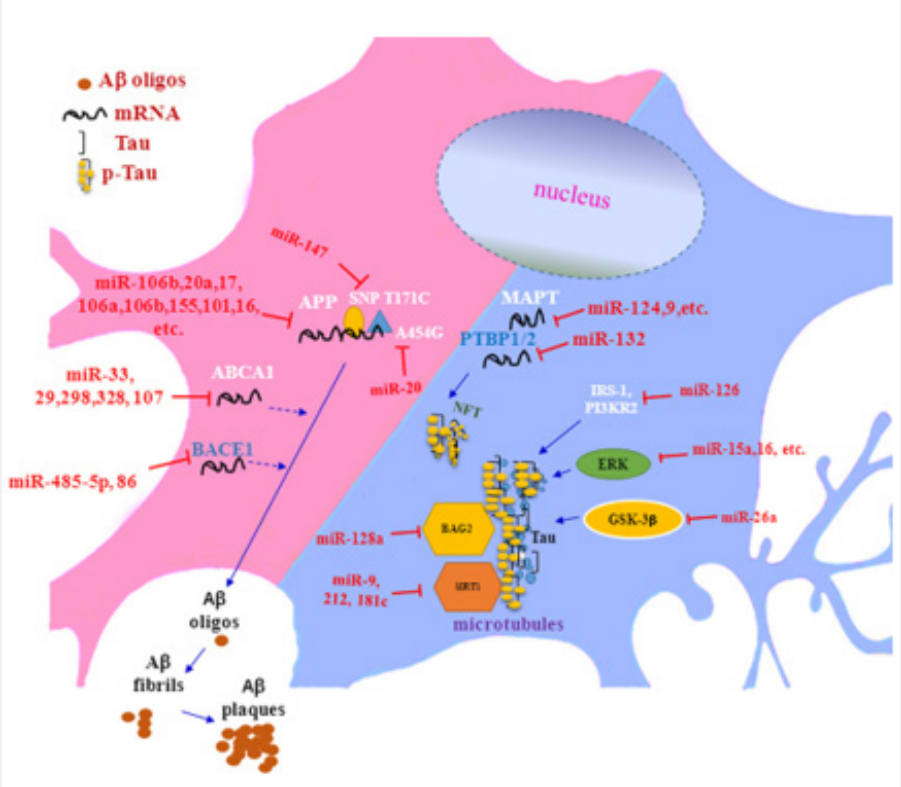

Figure 6: microRNA regulation in neurodegenerative diseases microRNAs and neuroinflammation. MicroRNAs are deeply involved in neurodegenerative disease pathways as shown in Figure 6. In Alzheimer's disease, dysregulated miRNAs modulate amyloid precursor protein (APP) processing and tau phosphorylation, directly influencing plaque and tangle formation. In Parkinson's disease, miRNAs regulate α synuclein aggregation, mitochondrial dysfunction, and neuroinflammation, contributing to dopaminergic neuron loss. In Huntington's disease, altered miRNAs affect transcriptional regulators and neuronal survival pathways, exacerbating neuronal death.
Source: [18]

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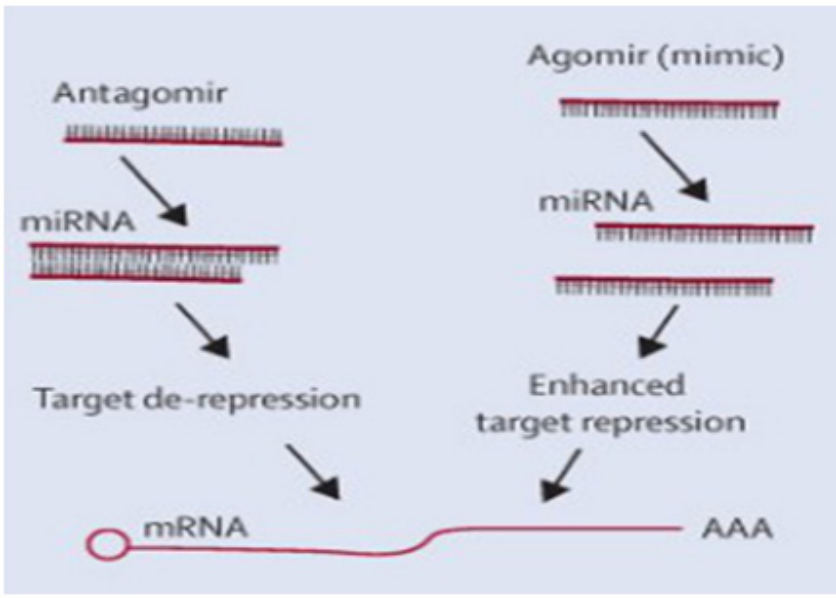

Figure 7: Therapeutic strategies targeting microRNAs. Therapeutic strategies targeting microRNAs in Figure 7 focus on restoring balance in gene regulation. Antagomirs are chemically engineered oligonucleotides that silence overexpressed oncomiRs, preventing them from driving proliferation, metastasis, or fibrosis. Conversely, miRNA mimics replenish lost tumor suppressor miRNAs, reinstating their protective roles in apoptosis, cell cycle control, and angiogenesis inhibition. Together, these approaches normalize dysregulated gene networks, offering precision therapies for cancer, cardiovascular disease, and neurodegeneration.
Sources: Esquela Kerscher & Slack (2006), Rupaimoole & Slack (2017).

Therapeutic applications of miRNA mimics and inhibitors are increasingly being explored, with several candidates advancing to clinical trials [1]. Many preclinical studies have demonstrated the efficacy of miRNA mimics in reducing tumor growth and improving responses to conventional therapies [2]. Utilizing miRNAs either as mimics or antagomirs presents a potent therapeutic strategy to interfere with key molecular pathways [3,4]. The strategy of miRNA therapeutics is based on restoring the balance of oncogenic and tumor-suppressor miRNAs [4].

Table 5 outlines current miRNA-based therapeutic strategies, their mechanisms and clinical development. miRNA mimics restore tumor suppressor function by replacing downregulated miRNAs and are preclinical to Phase I-II studies. Antagomirs and inhibitors silence oncogenic miRNAs and are at preclinical to early clinical stages. miRNA sponges act by sequestering multiple miRNAs simultaneously and remain in preclinical development. Nanoparticle delivery systems enable targeted delivery of mimics and inhibitors to improve stability and specificity and are now advancing toward clinical trials.

Challenges and Limitations of microRNA-Based Therapies

The biggest challenge for miRNA agents entering clinical practice is that naked miRNAs cannot be delivered to specific and targeted tissues [7]. Off-target gene silencing can cause potential toxicities and reduced therapeutic effects [8]. Several challenges exist for miRNA-based cancer therapeutics, including stability, toxicity, distribution, specificity to target tumor cells, and immunogenicity [9]. miRNA-based therapies face substantial challenges in clinical translation, including instability, degradation, and delivery inefficiency [10]. Despite their transformative potential, challenges persist, including off-target effects, immune activation, and delivery inefficiencies [11]. Key challenges include establishing miRNA sensitivity, specificity, and selectivity towards intended targets, while mitigating immunogenic reactions and off-target effects [12]. At present, two major challenges to miRNA drug development are the instability of nucleic acid molecules in vivo and the difficulty of developing efficient and safe drug delivery systems [12].

Table 6 highlights major challenges limiting the clinical translation of miRNA therapeutics and their potential solutions. Delivery challenges result in poor tissue targeting and are being addressed through nanoparticle and lipid nanoparticle (LNP) systems. Off-target effects can cause toxicity and unintended gene silencing, which may be mitigated by chemical modifications and AI-assisted design for improved specificity. Stability issues lead to rapid degradation of miRNA agents in vivo, countered by backbone modifications such as locked nucleic acid (LNA) and 2'-O-methyl

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modifications. Immune responses triggered by exogenous RNAs cause inflammation and adverse events, requiring carriers with reduced immunogenicity. Finally, regulatory hurdles slow approval due to lack of standards, which could be overcome by establishing standardized biomarkers and well-designed clinical trials.

Future Directions and Emerging Opportunities

Forward-looking solutions include smart detection platforms, nanocarrier-based precision delivery, and multi-omics integration [15]. The integration of non-viral delivery systems including lipid nanoparticles, PEI derivatives, and biomimetic carriers like exosomes has addressed critical challenges [15]. Artificial intelligence is reshaping the field, with deep learning models now predicting miRNA-mRNA interactions with >90% accuracy [15]. Gene-editing tools such as CRISPR-Cas9 are advancing precise regulation of miRNA expression, while AI and multi-omics approaches provide computational frameworks [15]. AI can accelerate safer, more targeted LNP design [16,17]. The convergence of CRISPR-based miRNA editing with multi-omics approaches enables systematic interrogation of miRNA regulatory networks [18,15]. Future directions emphasize precision medicine through patient-specific miRNA profiling, AI-assisted target prediction for optimized mimics/inhibitors, advanced nanoparticle delivery systems for enhanced specificity, CRISPR-miRNA integration for permanent correction, and multi-omics integration to map comprehensive regulatory networks, paving the way for safer, more effective therapies.

Conclusion

MicroRNAs have emerged as master regulators of gene expression through sophisticated post-transcriptional mechanisms involving precise biogenesis pathways and targeted mRNA silencing via the RISC complex. Their ability to fine-tune hundreds of target genes enables rapid cellular adaptation while maintaining homeostasis. In disease contexts, miRNAs play central roles across major pathologies. In cancer, they function as both oncomiRs and tumor suppressors, driving hallmark processes such as proliferation, apoptosis evasion, angiogenesis, and metastasis. In cardiovascular diseases, specific miRNAs orchestrate cardiac remodeling, hypertrophy, fibrosis, endothelial dysfunction, and atherosclerotic plaque formation. In neurological disorders, miRNA dysregulation contributes to neurodegeneration, protein aggregation, neuroinflammation, and neuronal death in conditions like Alzheimer's, Parkinson's, and Huntington's diseases. This widespread involvement underscores miRNAs as critical nodes in disease networks.

The therapeutic promise of miRNA-based interventions is substantial, with mimics restoring lost suppressor functions and inhibitors (antagomirs) silencing pathogenic miRNAs offering targeted precision medicine approaches. However, significant translational challenges remain, including efficient delivery to target tissues, off-target effects, stability in circulation, immunogenicity, and regulatory hurdles. Looking ahead, integration of advanced nanoparticle systems, AI-driven target prediction, CRISPR-miRNA editing, and multi-omics profiling holds immense potential to overcome these barriers. As research continues to mature, miRNA therapeutics are poised to transform the management of complex human diseases, shifting from conventional treatments toward personalized, mechanism-based strategies that address the root molecular dysregulation.

References

1. Ardekani AM, Naeini MM (2010) The Role of MicroRNAs in Human Diseases. Avicenna Journal of Medical Biotechnology 2(4): 161-179.
2. Azam HMH (2024) MicroRNA biomarkers in neurodegenerative diseases. Frontiers in Molecular Neuroscience.
3. Bhaskaran M, Mohan M (2013) MicroRNAs: History Biogenesis, and Their Evolving Role in Animal Development and Disease. Veterinary Pathology 51(4).
4. Chen KC, Wang YS (2012) MicroRNAs in atherosclerosis. The Kaohsiung Journal of Medical Sciences 28(12): 631-640.
5. Davis DBN, Hata A (2010) Mechanisms of control of microRNA biogenesis. Journal of Biochemistry 148(4): 381-392.
6. Di Leva G, Garofalo M, Croce CM (2014) MicroRNAs in cancer. Annual Review of Pathology. Mechanisms of Disease 9: 287-314.
7. Di Martino MT (2025) MicroRNA in cancer therapy: Breakthroughs and challenges. Journal of Experimental and Clinical Cancer Research 44(126).
8. Divakaran V, Mann DL (2008) The emerging role of microRNAs in cardiac remodeling and heart failure. Circulation Research 103(10): 1072-1083.
9. Fabian MR, Sonenberg N, Filipowicz W (2012) Regulation of mRNA translation and stability by microRNAs. Annual Review of Biochemistry 79: 351-379.
10. Gambari R, Brognara E, Spandidos DA, Fabbri E (2016) Targeting oncomiRNAs and mimicking tumor suppressor miRNAs: New trends in the development of miRNA therapeutic strategies in oncology. International Journal of Oncology 49(1): 5-32.
11. Guo S, Yiming W, Hongxin Z, Hongwei F, Yuan L, et al. (2025) Emerging frontiers in microRNA technology. Biomaterials 326: 123716.
12. Guo Y (2019) MicroRNAs in microglia. Frontiers in Molecular Neuroscience.
13. Iwakawa HO, Tomari Y (2015) The functions of microRNAs: mRNA decay and translational repression. Trends in Cell Biology 25(11): 651-665.
14. Johanson TM, Lew AM, Chong MMW (2013) MicroRNA biogenesis and regulation of bone marrow stromal cell function. Current Osteoporosis Reports 11(4): 331-338.
15. Ju J (2025) Challenges and opportunities in microRNA-based cancer therapeutics. Cell Reports Medicine 6(4): 102057.
16. Klicka K, Grzywa TM, Mielniczuk A, Klinke A, Włodarski PK, et al. (2022) The role of miR-200 family in the regulation of hallmarks of cancer. Frontiers in Oncology 12: 965231.
17. Kumar S (2014) Role of flow-sensitive microRNAs in endothelial dysfunction and atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology 34(10): 2206-2216.

How to cite this article: Okwah Micah N, Moses Adondua A, Ogbe Omale M, Kingsley Chimuanya U, Nkwocha John N, et al. MicroRNA-Mediated Gene Regulation in Human Diseases: Mechanisms, Therapeutic Applications, and Challenges. Int J Cell Sci & Mol Biol. 2026; 8(3): 555740. DOI:10.19080/IJCSMB.2026.08.555740

18. Letonja J (2024) A review of microRNAs and lncRNAs in atherosclerosis. Biomedicines 12(6): 1322.

19. Li S (2022) The role of microRNAs in neurodegenerative diseases. Frontiers in Molecular Neuroscience 39(1): 53-83.

20. Nobel Prize (2024) Advanced information. NobelPrize.org.

21. O'Brien J (2018) Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Frontiers in Endocrinology 9: 402.

22. O'Brien J, Hayder H, Zayed Y, Peng C (2018) Overview of microRNA biogenesis, mechanisms of actions, and circulation. Frontiers in Endocrinology 9: 402.

23. Orang AV, Safaralizadeh R, Kazemzadeh BM (2014) Mechanisms of miRNA-mediated gene regulation from common downregulation to mRNA-specific upregulation. International Journal of Genomics 2014: 970607.

24. Pandey S (2025) Exploring the therapeutic potential of microRNAs. Saudi Journal of Biological Sciences.

25. Reid G, Marissa W, Yuen YC, Kadir S, Patrick W, et al. (2025) Therapeutic potential of synthetic microRNA mimics based on the miR-15/107 consensus sequence. Cancer Gene Therapy 32: 486-496.

26. Seyhan AA (2024) Trials and tribulations of microRNA therapeutics. International Journal of Molecular Sciences 25(3): 1469.

27. Suzuki HI (2023) Roles of MicroRNAs in Disease Biology. Journal of the Japanese Medical Association 6(2): 104-113.

28. Svoronos AA, Engelman DM, Slack FJ (2016) OncomiR or tumor suppressor? The duplicity of microRNAs in cancer. Cancer Research 76(13): 3666-3670.

29. Telkoparan AP (2025) Emerging roles of microRNAs in cancer: From oncomiRs to tumor suppressors. Molecular Medicine Reports.

30. Tian H, Long C, Yunhui L, Hongyuan L, Miaomiao Q, et al. (2024) MicroRNA therapeutic delivery strategies: A review. Journal of Drug Delivery Science and Technology 93: 105430.

31. Topkara VK, Mann DL (2011) Role of microRNAs in cardiac remodeling and heart failure. Cardiovascular Research 25(2): 171-182.

32. Wang XH (2018) MicroRNAs of microglia. Journal of Neuroinflammation.

33. Wang Z, Hangxuan W, Shuhan Z, Jiasheng M, Zhiqing Z, et al. (2024) miRNA interplay: Mechanisms and therapeutic interventions in cancer. MedComm - Oncology 3(4): e93.

34. Wang Z, Yingyuan P, Haifeng Z, Min Z, Dianwen J, et al. (2025) MiRNA-based drugs: Challenges and delivery strategies. Applied Microbiology and Biotechnology 109(1): 247.

35. Zhang B, Pan X, Cobb GP, Anderson TA (2007). microRNAs as oncogenes and tumor suppressors. Developmental Biology 302(1): 1-12.

36. Zhao H, Junchao X, Xia G, Jingcheng Z, Zhongshan He, et al. (2026) Artificial intelligence in the rational design of lipid nanoparticles. The Innovation 1(1): 100006.

37. Abah MA, Umezurike KC, Nnaemeka NJ, Oladosu MA, Matthew OO, et al. (2026) Gene therapy for genetic disorders: A critical review of viral and non-viral delivery systems, challenges, and future prospects in treating monogenic diseases, cancer and infectious diseases. Drug and Pharmaceutical Science Archives 6(2): 15-26.

38. Yussuf MD, Ikedionu CA, Ocheinehi AJ, Ugwuanyi I, Olaoye EB, et al. (2025) Biodegradable Peptide Hydrogels for Precision Drug Release: Advances and Future Perspectives. European Journal of Scientific Research and Reviews 2 (3): 130-153.

39. Abubakar AA, TD Adeniyi, IO Nurain, AB Olanrewaju, KE Uthman, et al. (2019) Chromatographic and computational studies of ligands associated with bilharziasis. Talibah J Univ Med Sci 14 (2): 172-178.

40. Abah MA, MA Oladosu, OK Elijah, EP Chikelum, AB Olanrewaju, et al. (2025) The Evolving Role of Sodium-Glucose Linked Transporter-2 (SGLT2) Inhibitors in Heart Failure Management: A Paradigm Shift. Open J Cardiol Heart Dis 5(1).

41. Abah MA, Archibong EU, Oladosu MA, Chikelum EP, Ekekwe AC, et al. (2025) The protective role of sickle cell trait against Plasmodium falciparum malaria. J Hum Virol Retrovirol 12(1): 23-31.

42. Eze MN, Odoh HE, Apeh MC (2023) Assessment of Phytochemicals and Antioxidant Potential of the Stem Bark of Albizia Chevalieri. The Bioscientist Journal 11(1): 43-56.

43. Okwah MN (2022) Integrating Triglyceride-Glucose Index and Echocardiographic Parameters for Improved Cardiovascular Risk Stratification in Sub-Saharan Africa. International Journal of Cardiology 1(2): 1-16.

44. Farinde TD, Moses AA, Micheal AO, Ochuele DA, Njemanze OC, et al. (2025) The Impact of Plant-Based Diets on Cardiovascular Health: A Comprehensive Review. Plant Science Archives 10(4).

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DOI:10.19080/IJCSMB.2026.08.555740

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How to cite this article: Okwah Micah N, Moses Adondua A, Ogbe Omale M, Kingsley Chimuanya U, Nkwocha John N, et al. MicroRNA-Mediated Gene Regulation in Human Diseases: Mechanisms, Therapeutic Applications, and Challenges. Int J Cell Sci & Mol Biol. 2026; 8(3): 555740. DOI:10.19080/IJCSMB.2026.08.555740