Review

MicroRNA-221: A Context-Dependent Mediator in Human Diseases—From Molecular Mechanisms to Clinical Translation

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MicroRNA-221: A Context-Dependent Mediator in Human Diseases—From Molecular Mechanisms to Clinical Translation

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Highlights

What are the main findings?

1. miR-221 acts as a context-dependent mediator in diverse human diseases (including cancer, cardiovascular diseases, neurological disorders, etc.) by targeting key genes (e.g., PTEN, CDKN1C/p57) and regulating conserved signaling pathways (PI3K/AKT, TGF-β/SMAD).
2. Its function varies with disease type, cell/tissue origin, and genetic background—exerting oncogenic/tumor-suppressive effects in different cancers and protective/pathological roles in cardiovascular conditions—and it shows potential as a non-invasive biomarker for multiple diseases.

What are the implications of the main findings?

3. This review provides a comprehensive framework for understanding miR-221's multifaceted pathophysiological roles, supporting its utility as a diagnostic/prognostic biomarker across organ systems.
4. miR-221-targeting strategies hold preclinical promise for disease therapy, while highlighting the need to resolve context-dependent mechanisms and optimize cell-specific delivery systems for clinical translation.

Abstract

MicroRNA-221 (miR-221), a conserved small non-coding RNA, acts as a pivotal modulator of biological processes across multiple organ systems, the dysregulation of which is closely linked to the pathogenesis of various human diseases. This review systematically summarizes its multifaceted roles in cancer, cardiovascular diseases (CVDs), neurological disorders, digestive system diseases, respiratory conditions, and adipose-endocrine dysfunction. In cancer, miR-221 exerts context-dependent oncogenic/tumor-suppressive effects by targeting PTEN, CDKN1C/p57, Bmf, thereby regulating cell proliferation, invasion, stemness, and resistance to cancer therapy ; it also serves as a non-invasive biomarker for glioma, papillary thyroid carcinoma, colorectal cancer. In cardiovascular system, it balances antiviral defense in viral myocarditis, modulates ventricular fibrotic remodeling in heart failure, regulates endothelial function in atherosclerosis, with cell-type/ventricle-specific effects. In neurological disorders, it protects dopaminergic neurons in Parkinson's disease and modulates microglial activation in epilepsy. It also regulates hepatic pathogen defense, intestinal mucosal immunity. Mechanistically, miR-221 alters cellular phenotypes by targeting tumor suppressors or signaling components (e.g., PI3K/AKT, TGF-β/SMAD, Wnt/β-catenin).

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Therapeutically, miR-221-targeting strategies show preclinical promise in cancer and CVDs. Despite these progress, further studies are needed to resolve context-dependent functional discrepancies, validate biomarker utility, and develop cell-specific delivery systems. This review provides a framework to understand its pathophysiologcial roles and potential application as a biomarker and therapeutic target.

Keywords: miRNAs; miR-221; cardiovascular diseases; cancer; target genes; signaling pathway

1. Introduction

MicroRNAs (miRNAs), ~22-nucleotide non-coding RNAs, post-transcriptionally regulate gene expression by binding to the 3′ untranslated region (3′UTR) of target mRNAs, thereby mediating mRNA degradation or translational repression. Since their discovery, miRNAs have been implicated in nearly all biological processes, including cell cycle progression, apoptosis, differentiation, and metabolism, with their dysregulation driving the initiation and progression of numerous human diseases. Among these, miR-221 has garnered increasing attention due to its widespread involvement in disease pathogenesis across organ systems and its potential as a clinical biomarker and therapeutic target.

miR-221 is encoded within the human chromosome Xq11.2, and its expression is tightly controlled by transcriptional factors (e.g., NF-κB, β-catenin) and epitranscriptional modifications (e.g., m6A methylation by METTL3) [1,2]. Early studies highlighted miR-221's oncogenic role in cancer, where it was found to promote cell proliferation by targeting cyclin-dependent kinase inhibitors (CDKN1B/p27, CDKN1C/p57) [3,4]. A meta-analysis of 23 studies confirmed miR-221's diagnostic value across cancers, with a summary area under the receiver operating characteristic curve (AUC) of 0.82, supporting its utility as a liquid biopsy marker [5]. Beyond cancer, miR-221's role in cardiovascular health was first demonstrated in viral myocarditis (VM), where it restricts Coxsackievirus B3 (CVB3) replication and limits immunopathology by targeting pro-viral (IRF2) and pro-inflammatory (ETS1, CXCL12) genes; systemic inhibition of miR-221/-222 in mice exacerbated VM, leading to increased viral load and myocardial necrosis [6].

In neurological disorders, miR-221 emerged as a neuroprotective factor in Parkinson's disease (PD): the PD-linked protein DJ-1 upregulates miR-221 via the MAPK/ERK pathway, which then represses pro-apoptotic proteins (BIM, BMF) to protect dopaminergic neurons from oxidative stress [7]. In the digestive system, miR-221 modulates hepatic regeneration post-partial hepatectomy by targeting cell cycle inhibitors (p27, p57) and the transcription factor Arnt, accelerating hepatocyte S-phase entry [8]. These findings underscore miR-221's pleiotropy, but also reveal a critical feature: its function is context-dependent—shaped by disease type, cell/tissue origin, and genetic background. For example, in prostate cancer, miR-221 is upregulated in castration-resistant prostate cancer (CRPC) to promote androgen independence [9], yet downregulated in aggressive metastases, predicting clinical recurrence [10]. Similarly, in malignant meningioma, miR-221 inhibits radiation-induced invasiveness [11], whereas in breast cancer, it enhances invasion via Wnt/β-catenin activation [12].

Despite growing insights into miR-221's roles, several gaps remain: the molecular basis for its context-dependent function is not fully elucidated; its biomarker utility needs validation in large, multi-center clinical trials; and therapeutic strategies targeting miR-221 require optimization to minimize off-target effects. This review integrates current knowledge of miR-221's molecular mechanisms, disease-specific roles, biomarker potential, and therapeutic prospects across organ systems, aiming to provide a comprehensive resource for researchers and clinicians pursuing translational studies of miR-221.

2. The Role of MicroRNA-221 in Tumorigenesis, Progression, and Therapy: Mechanisms and Clinical Implications

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miR-221 has emerged as a pivotal regulator of tumor biology. Its dysregulation is widespread across human malignancies, where it exerts context-dependent oncogenic or, occasionally, tumor-suppressive effects. This section systematically dissect miR-221's roles in tumor initiation, progression, diagnosis, and therapy response, highlighting its molecular targets and signaling pathways across diverse cancer types.

2.1. miR-221 as a Diagnostic and Prognostic Biomarker in Human Cancers

miR-221's tissue- and circulation-specific expression patterns make it a promising biomarker for cancer detection and outcome prediction.

In glioma, plasma miR-221 levels are significantly elevated in patients compared to healthy controls, with a receiver operating characteristic (ROC) curve area under the curve (AUC) of 0.84 for distinguishing glioma from controls; high plasma miR-221 correlates with poor overall survival [5]. Additionally, exosomal miR-221 targets dynamin 3 (DNM3) to induce glioma progression and temozolomide resistance, further supporting its utility as a liquid biopsy marker [13].

In thyroid cancer, serum miR-221-3p distinguishes papillary thyroid carcinoma (PTC) from healthy controls [14]. During follow-up, a miR-221-3p fold change >2.2 reliably identifies progressive disease, even in patients with anti-thyroglobulin antibodies (TgAb) or residual thyroid tissue—contexts where thyroglobulin (Tg) is uninformative [14]. Transcriptional variations in miR-221 also modulate the microenvironment of thyroid cancer, further reinforcing its biomarker potential [15].

In colorectal cancer (CRC), miR-221 is upregulated in tumor tissues and stool samples. Stool-derived miR-221, alongside miR-18a, serves as a non-invasive diagnostic marker [16], while tissue miR-221 inhibits the cyclin-dependent kinase inhibitor CDKN1C/p57 to promote proliferation [3]. A feedback loop involving miR-221 maintains constitutive activation of NF-κB and STAT3 in CRC cells, linking its expression to inflammation-driven progression [17].

Other malignancies where miR-221 acts as a biomarker include pancreatic cancer (plasma miR-221-3p upregulation) [18], head and neck squamous cell carcinoma (bioinformatic analyses confirm miR-221-3p overexpression and oncogenic roles) [19], and esophageal cancer (miR-221 upregulation correlates with chemotherapy resistance) [20].

Notably, miR-221's biomarker utility is context-dependent. In prostate cancer, for example, miR-221 is upregulated in castration-resistant prostate cancer (CRPC) cell lines (e.g., LNCaP-Abl) to promote androgen independence [9], but its expression decreases in aggressive prostate cancer and metastases, predicting clinical recurrence [10]. This discrepancy underscores the need for cancer-type-specific validation.

2.2. miR-221 Regulates Tumor Cell Biology via Key Targets and Signaling Pathways

miR-221 modulates core hallmarks of cancer—cell proliferation, apoptosis, migration, and stemness—by inhibiting tumor suppressors and activating oncogenic pathways.

2.2.1. Proliferation and Cell Cycle Control

In cutaneous squamous cell carcinoma (CSCC), miR-221 is upregulated in tissues and cell lines (SCC13, A431); its knockdown arrests cells in G0/G1 phase and reduces colony formation, while overexpression accelerates G1/S transition [21]. Mechanistically, miR-221 directly targets phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/AKT pathway, leading to increased AKT phosphorylation and upregulation of cyclin D1 [21].

In hepatocellular carcinoma (HCC), miR-221 exerts dual effects via distinct targets. It inhibits CDKN1C/p57 and CDKN1B/p27 (cell cycle inhibitors) to promote proliferation[3,4], and targets histone deacetylase 6 (HDAC6) to enhance malignant progression [22]. A transgenic mouse model confirmed miR-221's oncogenic role: liver-specific miR-221 overexpression promotes tumorigenesis [23]. Additionally, miR-221 targets Bmf (a pro-apoptotic Bcl-2 family member) in HCC, correlating with tumor multifocality [24].

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In neuroblastoma, miR-221 enhances MYCN oncoprotein levels by targeting Nemo-like kinase (NLK), a negative regulator of MYCN; high miR-221 expression correlates with advanced disease and poor prognosis[25] .

2.2.2. Migration, Invasion, and Metastasis

In breast cancer, miR-221 drives multiple aggressive phenotypes. It activates the Wnt/β-catenin pathway to promote triple-negative breast cancer (TNBC) progression [12], and targets PTEN to enhance cancer stem cell (CSC)-like properties—including mammosphere formation and tumor initiation [26]. miR-221 also confers resistance to fulvestrant (an anti-estrogen) by regulating estrogen receptor (ER) signaling and downstream effectors [27].

In colon cancer, activation of M3 muscarinic receptors (M3R) triggers the PKC/p38 MAPK pathway, inducing miR-221/222 expression; miR-221 then upregulates matrix metalloproteinases (MMPs) to enhance invasion [28]. Similarly, in osteosarcoma, miR-221 modulates migration and invasion by targeting yet-to-be-identified tumor suppressors [29].

Conversely, in malignant meningioma, miR-221/222 inhibits radiation-induced invasiveness by downregulating pro-metastatic genes, highlighting its context-dependent role in migration [11].

2.2.3. Stem Cell-like Properties

In breast CSCs, miR-221/222 targeting of PTEN activates the PI3K/AKT pathway, increasing the CD44+/CD24− CSC population and tumorigenicity [26]. In breast cancer stem cells under hypoxia, β-catenin binds miR-221 to downregulate Rad51 (a DNA repair gene) and ERα, sustaining a pro-inflammatory phenotype that promotes self-renewal [30].

In glioma CSCs, exosomal miR-221 from tumor cells targets DNM3 to enhance stemness and temozolomide resistance, creating a pro-tumorigenic microenvironment[13] .

2.3. miR-221 Mediates Cancer Therapy Resistance

miR-221 contributes to resistance against chemotherapy and radiotherapy, posing a barrier to effective cancer treatment.

2.3.1. Chemoresistance

In breast cancer, METTL3 (an m6A methyltransferase) accelerates pri-miR-221-3p maturation in an m6A-dependent manner, leading to adriamycin resistance in MCF-7 cells [31]. miR-221 also confers fulvestrant resistance by regulating ER signaling and downstream pathways (e.g., PI3K/AKT)[27] .

In glioma, exosomal miR-221 induces temozolomide resistance by targeting DNM3, which normally suppresses DNA repair[9]. In esophageal cancer, miR-221 mediates chemotherapy resistance via mechanisms likely involving PTEN downregulation [20].

In HCC, miR-221's effect on chemosensitivity depends on p53 status. In p53-wild-type cells, miR-221 activates the p53/MDM2 feedback loop to enhance doxorubicin-induced apoptosis; in p53-mutant cells, it promotes resistance [4].

2.3.2. Radiosensitivity

In malignant meningioma, miR-221/222 enhances radiosensitivity by inhibiting radiation-induced invasiveness, possibly via downregulating MMPs [11]. In glioma, knockdown of miR-221 increases radiosensitivity by restoring Rad51 expression, impairing DNA repair [5].

2.3.3. Targeting miR-221 for Cancer Therapy

Strategies to inhibit miR-221 or combine it with other therapies show promise in preclinical models.

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In HCC, co-administration of miR-122 mimics (a tumor suppressor) and miR-221 inhibitors synergistically reduces tumor growth by restoring PTEN and p27 expression [32]. In glioma, a doxorubicin-conjugated miR-221 molecular beacon (miR-221 DOXO MB) achieves theranosis: it detects endogenous miR-221 via fluorescence activation, inhibits miR-221 function, and releases doxorubicin to induce cytotoxicity in C6 cells and nude mouse xenografts [33].

In CRC, ferulic acid-loaded polymeric micelles enhance anti-cancer activity by activating TP53INP1 (a p53 target) via miR-221 inhibition [34]. In prostate cancer, targeting the lncRNA MIR222HG—co-transcribed with the miR-221/-222 cluster—reduces CRPC progression by downregulating miR-221[35].

In summary, miR-221 is a multifunctional regulator of tumor biology, with its role dictated by cancer type, stage, and genetic background. Its overexpression drives proliferation, invasion, and therapy resistance in most malignancies, often via targeting PTEN, CDKN1C/p57, or MDM2. As a biomarker, miR-221 enables non-invasive diagnosis and prognosis in glioma, PTC, and CRC. Therapeutic strategies targeting miR-221, such as molecular beacons or combination with miR-122 mimics, hold translational potential. Future studies should focus on dissecting miR-221's interactions with the tumor microenvironment and validating its utility in clinical trials.

3. The Biological Functions of MicroRNA-221 in the Cardiovascular System: Insights from Preclinical and Clinical Studies

3.1. miR-221 in Viral Myocarditis: Balancing Antiviral Defense and Inflammatory Homeostasis

Viral myocarditis (VM), a leading cause of heart failure (HF) and sudden cardiac death in young adults, is characterized by viral replication in cardiomyocytes and excessive inflammatory responses. The miR-221/222 cluster emerges as a key mediator of this pathological process. In a landmark study using Coxsackievirus B3 (CVB3)-induced murine VM, Corsten et al. demonstrated that miR-221 levels are significantly elevated in the acute phase of infection, with expression predominantly restricted to cardiomyocytes (rather than infiltrating CD45+ immune cells) [6]. Systemic inhibition of miR-221/222 via antagomiRs resulted in a 3-fold increase in cardiac CVB3 genome copies, prolonged viremia (viral titres remained detectable in plasma at day 4 post-infection vs. clearance in controls), and severe myocardial necrosis (necrotic area increased from 31% to 52% in C3H mice) [6]. Mechanistically, miR-221 directly targets a network of pro-viral and pro-inflammatory genes, including ETS1/2 (transcription factors promoting cytokine and chemokine expression), IRF2 (a suppressor of type I interferons), and CXCL12 (a chemokine driving T-cell infiltration), thereby restricting viral replication and limiting immunopathology [6]. In vitro, overexpression of miR-221 in neonatal rat cardiomyocytes (NRCMs) inhibited CVB3 replication by ~50% at 72 h post-infection, while knockdown enhanced viral load, confirming its antiviral role [6].

3.2. miR-221 in Heart Failure: Ventricular Specificity and Fibrotic Remodeling

Heart failure exhibits distinct molecular signatures between the left (LV) and right (RV) ventricles, and miR-221 contributes to this regional heterogeneity. In a canine tachypacing-induced biventricular HF model, Powers et al. observed that miR-221 was selectively upregulated (2-fold) in the failing RV but not LV, correlating with more extensive RV fibrosis (collagen content: 20% vs. 12% in LV) [36]. This RV-specific upregulation was driven by fibroblasts: RV fibroblasts (but not LV fibroblasts or cardiomyocytes) showed robust miR-221 induction in response to cyclic overstretch (mimicking pressure overload) and aldosterone (a neurohormone elevated in HF), with miR-221 levels increasing by ~3-fold and 2.5-fold, respectively [36]. Functional studies revealed that miR-221 knockdown via anti-miRs significantly attenuated RV fibroblast proliferation (by ~40%) and collagen production, whereas LV fibroblasts remained unresponsive, highlighting cell-type and ventricle-specific effects[36].

In pressure overload-induced HF, miR-221 plays a protective role against fibrotic remodeling. Verjans et al. reported that miR-221 expression was downregulated in myocardial biopsies from

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patients with dilated cardiomyopathy (DCM) or aortic stenosis (AOS) with severe fibrosis, with levels inversely correlating with collagen volume fraction and LV stiffness [37]. In mice, inhibition of miR-221 exacerbated Angiotensin II (AngII)-induced cardiac fibrosis (interstitial collagen content increased by ~60%) and LV dysfunction (ejection fraction decreased by ~25%), without affecting cardiac hypertrophy [37]. Mechanistically, miR-221 targets multiple components of the TGF-β/SMAD signaling pathway, including ETS1 (a co-activator of TGF-β-induced collagen synthesis), JNK1 (a stress kinase promoting fibroblast activation), and TGF-β receptors 1/2 (TGF-βR1/2), thereby restricting profibrotic signaling [37]. Conversely, miR-221 can also promote HF progression via autophagy inhibition: Su et al. showed that miR-221 suppresses autophagy in cardiomyocytes by targeting p27 (a cyclin-dependent kinase inhibitor), leading to accumulation of damaged organelles as well as cardiac dysfunction [38]. Additionally, METTL3 (an m6A methyltransferase) mediates Ang II-induced cardiac hypertrophy by accelerating pri-miR-221 maturation in an m6A-dependent manner, linking epitranscriptional regulation to miR-221-driven pathological remodeling [1].

3.3. miR-221 in Coronary Artery Disease and Atherosclerosis

Coronary artery disease (CAD) and atherosclerosis are driven by dysregulated immune responses and endothelial dysfunction, processes modulated by miR-221. Torres-Paz et al. found that miR-221-5p is overexpressed in monocytes from Mexican CAD patients , and this overexpression is associated with a 6.4-fold increased risk of CAD [39]. Mechanistically, miR-221 downregulates PTEN (a phosphatase inhibiting the PI3K/AKT pathway), leading to enhanced monocyte activation and reduced expression of endothelial nitric oxide synthase (NOS3)—a key regulator of vascular relaxation [39]. Notably, metformin (an antidiabetic drug with cardioprotective effects) reduced miR-221 expression in CAD patients, coinciding with decreased monocyte inflammation and improved endothelial function [39].

In endothelial cells, miR-221 protects against atherosclerosis-related injury. Qin et al. showed that oxidized low-density lipoprotein (ox-LDL)—a major driver of endothelial dysfunction—downregulates miR-221 in human umbilical vein endothelial cells (HUVECs) by ~40% at 48 h post-treatment [40]. Overexpression of miR-221 protected HUVECs from ox-LDL-induced apoptosis (caspase-3 activity reduced by ~50%) by inhibiting ETS1 and its downstream target p21 (a cyclin-dependent kinase inhibitor promoting cell cycle arrest) [40]. Similarly, miR-221 regulates endothelial nitric oxide (NO) production and inflammation by targeting adiponectin receptor 1 (AdipoR1): Chen et al. demonstrated that miR-221 overexpression in HUVECs reduces AdipoR1 expression by ~60%, leading to decreased NO production and increased pro-inflammatory cytokine release (TNF-α and IL-6) [41].

Atherosclerosis progression is also modulated by lncRNA-miR-221 crosstalk. LincRNA-p21, a known tumor suppressor, alleviates atherosclerosis by sequestering miR-221: Zhang et al. showed that lincRNA-p21 expression is downregulated in atherosclerotic plaques, and overexpression of lincRNA-p21 increases miR-221 targets (e.g., p27) and reduces macrophage foam cell formation [42]. Additionally, M2 macrophage-derived extracellular vesicles (EVs) protect against abdominal aortic aneurysm (AAA) by delivering miR-221-5p, which modulates macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotype, reducing aortic wall inflammation and elastin degradation [43].

3.4. miR-221 in Vascular Regeneration and Stem Cell Differentiation

miR-221 plays a critical role in vascular regeneration by regulating stem cell differentiation and endothelial function. Gao et al. demonstrated that miR-221/222 promote endothelial differentiation of adipose-derived stem cells (ADSCs) by targeting PTEN, activating the PI3K/AKT/mTOR pathway [44]. Overexpression of miR-221 in ADSCs increased the expression of endothelial markers (CD31, CD34, and CD144 by ~2–3-fold), enhanced low-density lipoprotein (LDL) uptake (by ~40%), and improved tube formation in vitro [44]. In a rat model of hindlimb ischemia, intramuscular injection

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of miR-221-overexpressing ADSCs significantly improved blood perfusion and reduced inflammatory infiltration [44].

Endothelial progenitor cells (EPCs), key players in vascular repair, are also regulated by miR-221. Eicosapentaenoic acid (EPA), an omega-3 fatty acid, induces neovasculogenesis in human EPCs by modulating c-kit protein and the PI3-K pathway, with miR-221 acting as a downstream mediator: EPA treatment upregulates miR-221 by ~2-fold, enhancing EPC proliferation and migration [45]. Similarly, docosahexaenoic acid (DHA) alleviates trimethylamine-N-oxide (TMAO)-mediated impairment of EPC neovascularization by restoring miR-221 levels, which are downregulated by TMAO (by ~50%) [46]. However, senescent mesenchymal stem cells (MSCs) release exosomes with downregulated miR-221-3p, impairing heart repair after myocardial injury: Wang et al. showed that exosomal miR-221-3p from senescent MSCs reduces cardiomyocyte survival by ~30% in vitro, whereas supplementation with miR-221-3p mimics rescues this effect [47].

3.5. miR-221 in Myocardial Ischemia-Reperfusion Injury

Myocardial ischemia-reperfusion (I/R) injury, a complication of revascularization therapies, is modulated by miR-221 in a context-dependent manner. Meng et al. reported that miR-221-3p is upregulated in H2O2-treated H9c2 cardiomyocytes (a model of oxidative stress) and in the ischemic region of rat I/R hearts [48]. Overexpression of miR-221-3p increased cardiomyocyte necrosis (propidium iodide-positive cells by ~60%) and lactate dehydrogenase (LDH) release (by ~50%), while the knockdown of which reduced cell death [48]. Mechanistically, miR-221-3p directly targets p57 (a cyclin-dependent kinase inhibitor with cardioprotective effects), and overexpression of p57 reversed miR-221-3p-induced myocardial damage in vitro and in vivo [48]. In contrast, Zhang et al. showed that miR-221 overexpression in a rat MI model reduces infarct size (by ~30%) and fibrosis (by ~25%), improving cardiac function via targeting of pro-fibrotic genes [49].

3.6. miR-221 in Vascular Smooth Muscle Cells and Vein Graft Disease

Vascular smooth muscle cell (VSMC) phenotype switching and neointimal hyperplasia are key processes in vein graft disease, regulated by miR-221. Platelet-derived growth factor (PDGF) signaling induces miR-221 expression in VSMCs, which is critical for modulating VSMC phenotype from contractile to synthetic: Wang et al. demonstrated that PDGF-BB upregulates miR-221 by ~3-fold, downregulating p27 and promoting VSMC proliferation [50]. In a rat vein graft model, miR-221 sponge therapy (a miR inhibitor) attenuated neointimal hyperplasia (neointimal area reduced by ~50%) and improved blood flow (by ~40%), by inhibiting VSMC proliferation and migration [51]. Furthermore, miR-221 inhibits latent TGF-β1 activation through targeting thrombospondin-1 (TSP-1), a key activator of TGF-β1, thereby attenuating kidney failure-induced cardiac fibrosis. miR-221 overexpression in a rat model of chronic kidney disease reduces TSP-1 expression by ~60%, leading to decreased TGF-β1 activation and collagen deposition [52].

3.7. miR-221 as a Biomarker in Cardiovascular Diseases

miR-221 has emerged as a potential biomarker for various cardiovascular conditions. In hypertrophic obstructive cardiomyopathy (HOCM), miR-221 levels are upregulat1ed in myocardial tissue (by ~2-fold) and plasma (by ~1.8-fold), correlating with myocardial hypertrophy and fibrosis, making it a promising diagnostic biomarker [53].

In summary, miR-221 exerts multifaceted roles in the cardiovascular system, acting as a protective mediator in viral myocarditis, vascular regeneration, and MI, while promoting pathological remodeling in HF, I/R injury, and atherosclerosis—depending on the disease context, target cell type, and upstream regulators. Its ability to target key pathways (PTEN/PI3K/AKT, TGF-β/SMAD, ETS1/p21) and molecules (STAT5A, p57, AdipoR1) highlights its therapeutic potential. Future studies should focus on developing cell-specific miR-221 modulators to harness its protective

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effects while minimizing off-target risks, and validating its role as a biomarker in large-scale clinical trials.

4. miR-221 in the Nervous System: Multifaceted Biological Functions

miR-221 exerts critical regulatory roles in the nervous system, governing neuronal survival, neuroinflammation, and nerve regeneration through context-specific mechanisms. In neuronal protection against oxidative stress and neurodegeneration, miR-221 acts as a downstream effector of the Parkinson's disease (PD)-linked protein DJ-1. Wild-type DJ-1, but not its pathogenic M26I mutant, upregulates miR-221 via the MAPK/ERK pathway; miR-221 then represses pro-apoptotic proteins (e.g., BIM, BMF, FOXO3a) to protect dopaminergic neurons from MPP^+-induced death and neurite retraction [7]. Consistently, in 6-OHDA-induced PD mice, miR-221 overexpression targets BIM, inhibits the Bax/caspase-3 apoptotic pathway, rescues dopamineergic neuron loss, and improves motor function [54]. Additionally, nerve growth factor (NGF) induces miR-221 in PC12 cells via sustained ERK1/2 activation, which downregulates BIM to enhance neuronal survival [55].

In neuroinflammation regulation, miR-221 modulates microglial activation. In valproic acid-resistant epilepsy, miR-221-3p is downregulated; its mimic reduces hypoxia-inducible factor-1α (HIF-1α) expression, suppressing microglial polarization to the proinflammatory M1 phenotype and alleviating seizure severity [56]. Similarly, propofol exerts anti-inflammatory effects by downregulating miR-221/222, which directly targets interferon regulatory factor 2 (IRF2); this restores IRF2 levels, inhibiting LPS-induced microglial activation and proinflammatory cytokine (IL-1β, TNF-α) release [57].

In peripheral nerve regeneration, miR-221/222 delivered via a biodegradable PDAPEI vector promotes Schwann cell proliferation and function. It upregulates nerve growth factor (NGF) and myelin basic protein (MBP) expression, enhancing remyelination and functional recovery (e.g., increased nerve conduction velocity, improved sciatic function index) after sciatic nerve crush injury [58].

Collectively, miR-221 emerges as a key modulator of neuronal health, inflammation, and repair, with therapeutic potential for neurodegenerative diseases, epilepsy, and peripheral nerve injury.

5. miR-221 in the Digestive System: Multifaceted Biological Functions

miR-221 exerts diverse regulatory roles in the digestive system, modulating cellular homeostasis, inflammation, regeneration, and pathogen-host interactions across liver and intestinal tissues.

In the liver, miR-221 participates in pathogen defense and cell survival. During bovine viral diarrhoea virus (BVDV) infection, bta-miR-221 is significantly downregulated in Madin–Darby bovine kidney (MDBK) cells. This reduction relieves repression of its target autophagy-related gene ATG7, activating the ATG7-LC3 autophagy pathway to enhance viral replication; conversely, bta-miR-221 overexpression inhibits BVDV proliferation by suppressing ATG7 and autophagy [59]. In fulminant liver failure, miR-221 acts as a cytoprotective factor: it is upregulated in response to FAS-induced apoptosis, directly targeting the proapoptotic Bcl-2 family member PUMA to reduce hepatocyte death. Adeno-associated virus (AAV8)-mediated miR-221 overexpression delays liver failure in mice by lowering serum transaminases and TUNEL-positive cells [60]. Additionally, miR-221 accelerates liver regeneration post partial hepatectomy: it targets Arnt (a bHLH/PAS transcription factor), p27, and p57 (cell cycle inhibitors) to promote hepatocyte S-phase entry, increasing Ki67/PCNA-positive cells and cyclin (D1, E1, A2) expression [8].

In chronic liver injury and fibrosis, miR-221 is a key regulator and biomarker. It is upregulated in hepatic stellate cells (HSCs) and fibrotic livers (from hepatitis C, NASH, or CCl_4-induced models), targeting Gnai2 (reducing CCL2 secretion) and SOCS1 (alleviating inflammation) to mitigate fibrosis. Serum miR-221 levels correlate with fibrosis stage, serving as a noninvasive biomarker for cirrhosis and hepatocellular carcinoma (HCC) [61]. Mechanistically, miR-221/222 expression in HSCs is

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regulated by NF-κB; TGF-α/TNF-α induce miR-221, which targets CDKN1B (p27) to promote HSC activation, while NF-κB inhibitors reverse this effect [2]. Moreover, miR-221/222 exacerbate hepatic inflammation by repressing TIMP-3 (a TNF-α-converting enzyme inhibitor), amplifying proinflammatory signaling [62].

In the intestine, miR-221 modulates mucosal immunity. As a negative feedback regulator downstream of IL-23, it targets Maf (a Th17 transcription factor) and IL23R (IL-23 receptor) to constrain proinflammatory Th17 cell expansion. miR-221 deficiency increases IL-17A production in intestinal $CD4^+$ T cells, exacerbating DSS-induced colitis, while T cell-specific miR-221 deletion enhances mucosal damage [63].

6. miR-221 in the Respiratory System: Multifunctional Regulatory Roles

miR-221 plays critical context-dependent roles in the respiratory system, governing cell survival, inflammation, vascular remodeling, and airway homeostasis.

In lung epithelial protection against heavy metal toxicity, manganese (Mn^{2+}) exposure downregulates miR-221-3p in BEAS-2B and A549 cells, inducing reactive oxygen species (ROS) generation, cell cycle arrest, and apoptosis. Forced overexpression of miR-221-3p reverses these effects, improving cell viability and reducing Mn^{2+}-mediated cytotoxicity [64]. In pulmonary inflammation regulation, wild bitter gourd fruit extract (WBGE) upregulates miR-221/-222 to inhibit the PI3K/AKT/NF-κB pathway, decreasing intercellular adhesion molecule-1 (ICAM-1) expression and monocyte adhesion; this anti-inflammatory effect is abolished in miR-221/-222 knockout mice, confirming miR-221's mediating role [65].

In pulmonary arterial hypertension (PAH), miR-221-3p is upregulated in lung tissues and pulmonary arterial smooth muscle cells (PASMCs). It directly targets AXIN2, a negative regulator of Wnt/β-catenin signaling, to promote PASMC proliferation. Intravenous miR-221-3p inhibitor reduces right ventricular systolic pressure and vascular remodeling, attenuating PAH progression [66]. In asthma, miR-221 drives airway remodeling via the PI3K/AKT pathway: inhibiting miR-221 in ovalbumin-induced asthmatic mice decreases airway hyperresponsiveness, mucus metaplasia, and collagen deposition [67]. In severe asthma, miR-221 specifically regulates airway smooth muscle cell (ASMC) hyperproliferation by targeting cyclin-dependent kinase inhibitors p21WAF1 and p27kip1, though it does not affect corticosteroid insensitivity [68].

In LPS-induced acute lung injury (ALI), miR-221 upregulation exacerbates inflammation and apoptosis. Its inhibition upregulates suppressor of cytokine signaling 1 (SOCS1), inactivating NF-κB to reduce proinflammatory cytokines (IL-6, TNF-α) and improve lung permeability [69]. Collectively, miR-221 emerges as a pivotal target for respiratory disorders, from toxicity resistance to inflammatory and remodeling-related diseases.

7. miR-221 in Adipose and Endocrine Systems: Biological Functions

miR-221 exerts pleiotropic roles in the adipose and endocrine systems, regulating lipid metabolism, hormone signaling, and metabolic disease-related processes, as supported by recent studies.

In the adipose system, miR-221 modulates lipid homeostasis and adipocyte function through multiple targets. It cooperates with the RNA-binding protein PTB to repress the translation of adiponectin receptor 1 (AdipoR1) by binding its 3'UTR; in genetic and dietary obesity models, upregulated miR-221 (and PTB) reduces AdipoR1 protein levels, impairing adiponectin signaling and insulin sensitivity [70]. In inflamed adipocytes, miR-221 is induced by LPS-stimulated macrophage-conditioned medium, directly targeting angiopoietin-like 8 (ANGPTL8)—a key lipid metabolism regulator. This repression correlates with reduced triglyceride storage in adipocytes, and a significant negative correlation between miR-221 and ANGPTL8 is observed in subcutaneous adipose tissue (SAT) of morbidly obese subjects, which vanishes post-bariatric surgery [71]. Additionally, in mammary epithelial cells (MECs), miR-221 inhibits lipid synthesis by downregulating fatty acid

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synthase (FASN); estradiol and progesterone decrease miR-221 expression to promote lipid accumulation, and its low expression during lactation suggests a role in milk lipid production [72]. In human adipose tissue, miR-221 is upregulated in obesity, acting downstream of leptin and TNF-α to disrupt fat metabolism [73], while miR-221-3p also regulates human adipocyte differentiation and the composition of disease-relevant lipids, linking it to metabolic dysfunction [74].

In the endocrine system, miR-221 mediates glucose-related pathologies and hormone-dependent processes. In diabetic wound healing, miR-221-3p targets thrombospondin 1 (THBS1)—an anti-angiogenic factor—to reduce keratinocyte apoptosis and enhance endothelial tube formation, accelerating wound closure in diabetic mice; its knockout delays healing and increases THBS1 expression [75]. It also alleviates high glucose-induced inflammation in keratinocytes by targeting dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), inhibiting STAT3 phosphorylation (Tyr705/Ser727) and reducing proinflammatory cytokines (IL-1β, IL-6) [76]. In the ovary, miR-221 is hormonally regulated in theca and granulosa cells, where it modulates ovarian steroidogenesis and follicular development[77]. Furthermore, human polynucleotide phosphorylase (hPNP) selectively degrades miR-221, controlling its intracellular levels to fine-tune its regulatory effects in endocrine and metabolic tissues [78].

Collectively, miR-221 acts as a critical node in adipose lipid metabolism and endocrine homeostasis, with its dysregulation contributing to obesity, diabetes, and ovarian dysfunction—highlighting its potential as a therapeutic target.

8. Conclusions

miR-221 has established itself as a key context-dependent mediator of human disease, with its function shaped by tissue/cell type, disease stage, and genetic background. This review synthesizes evidence that miR-221 modulates core biological processes—including cell proliferation, apoptosis, inflammation, and remodeling—across major organ systems, primarily via targeting tumor suppressors (PTEN, CDKN1C/p57, et al.) and signaling pathway components (ETS1, AXIN2, TGF-βR1/2, et al.) to alter cellular phenotypes (Table1).

In cancer, miR-221's dual role (oncogenic/tumor-suppressive) is most evident: it drives proliferation and therapy resistance in glioma, breast, and hepatocellular carcinoma [13,22,31], yet predicts favorable outcomes in aggressive prostate cancer metastases [10]. Its utility as a non-invasive biomarker is supported by consistent associations with disease diagnosis (e.g., stool miR-221 for colorectal cancer [16]) and prognosis (e.g., plasma miR-221 for glioma [5], with a meta-analysis confirming its broad diagnostic value (summary AUC = 0.82) [5]. Therapeutically, strategies such as miR-221 inhibitors combined with miR-122 mimics [32] or doxorubicin-conjugated molecular beacons [33] have shown preclinical efficacy, highlighting potential for cancer treatment.

In the cardiovascular system, miR-221's cell-type specificity is striking: it protects cardiomyocytes from viral injury in VM [6], restricts fibrotic remodeling in pressure overload-induced heart failure [37], and regulates endothelial function in atherosclerosis [40]. However, it can also promote pathological remodeling—e.g., by inhibiting autophagy in cardiomyocytes [38] or driving pulmonary arterial smooth muscle cell proliferation in pulmonary arterial hypertension [66]. This duality emphasizes the need for cell-specific targeting to harness miR-221's protective effects while mitigating deleterious side-effects.

Across other systems, miR-221's roles are equally diverse: it protects dopaminergic neurons in PD [7], modulates hepatic regeneration [8], restricts intestinal inflammation [63], and regulates adipose lipid metabolism [70]. Common mechanisms—such as modulation of PI3K/AKT and TGF-β/SMAD pathways—link these roles, suggesting conserved regulatory networks that could be targeted across diseases.

Table 1. Key Target Genes and Signaling Pathways of miR-221.

System/Disease Type	Key Target Genes	Regulated Signaling Pathways	Functional Effects	Ref

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Oncological System				
Glioma	DNM3	DNA repair and tumor progression	Promotes glioma proliferation and temozolomide resistance; serves as a liquid biopsy marker	[13]
Cutaneous Squamous Cell Carcinoma (CSCC)	PTEN	PI3K/AKT pathway	Accelerates G1/S phase transition, promotes cell proliferation and colony formation	[21]
Hepatocellular Carcinoma (HCC)	CDKN1C/p57, CDKN1B/p27	Cell cycle regulatory pathway	Inhibits cell cycle inhibitors to promote hepatocyte proliferation	[3,4]
Hepatocellular Carcinoma (HCC)	HDAC6	malignant progression of tumors	Enhances the malignant phenotype of HCC cells	[22]
Hepatocellular Carcinoma (HCC)	Bmf	Bcl-2 family apoptotic pathway	Inhibits pro-apoptotic proteins; associated with tumor multifocality	[24]
Neuroblastoma	NLK	MYCN regulatory pathway (NLK is a negative regulator of MYCN)	Increases MYCN levels; associated with disease progression and poor prognosis	[25]
Triple-Negative Breast Cancer (TNBC)	PTEN	Wnt/β-catenin, PI3K/AKT pathways	Activates pathways to promote tumor progression and cancer stem cell (CSC) properties	[26]
Colorectal Cancer (CRC)	CDKN1C/p57	Cell cycle regulatory pathway	Inhibits p57 to promote cell proliferation	[3]
Colorectal Cancer (CRC)	TP53INP1	p53 signaling pathway	Inhibits TP53INP1 to weaken p53-mediated tumor-suppressive effects; ferulic acid-loaded micelles activate TP53INP1 by inhibiting miR-221	[34]
Esophageal Cancer (Chemoresistant)	DKK2	chemoresistance-related phenotypes	Mediates chemotherapy resistance	[20]
Cardiovascular System				
Viral Myocarditis (VM)	ETS1/2, IRF2, BCL2L11, TOX, BMF, CXCL12	Antiviral defense pathway, Inflammatory regulation pathway	Restricts CVB3 replication, reduces T-cell infiltration and myocardial necrosis	[6]
Heart Failure (HF, Autophagy Regulation)	p27	p27/CDK2/mTOR pathway	Inhibits p27 to block autophagy, leading to accumulation of damaged organelles and cardiac dysfunction	[38]

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Coronary Artery Disease (CAD)	AdipoR1	Adiponectin signaling pathway, NO production pathway	Inhibits AdipoR1 to reduce NO production and increase pro-inflammatory cytokine release	[41]
Vascular Regeneration (Adipose-Derived Stem Cells)	PTEN	PI3K/AKT/mTOR pathway	Activates the pathway to promote endothelial differentiation and angiogenesis	[44]
Myocardial Ischemia-Reperfusion (I/R) Injury	p57	cardiomyocyte survival	Inhibits p57 to increase cardiomyocyte necrosis and LDH release	[48]
Vascular Smooth Muscle Cell (VSMC) Phenotypic Switching	p27Kip1	PDGF signaling pathway	Downregulates p27Kip1 to promote VSMC switching from contractile to synthetic phenotype	[50]
Renal Failure-Associated Cardiac Fibrosis	TSP-1	TGF-β activation pathway (TSP-1 is an activator of TGF-β)	Inhibits TSP-1 to reduce TGF-β1 activation and collagen deposition	[52]
Nervous System				
Parkinson's Disease (PD)	BIM	Bax/caspase-3 apoptotic pathway	Inhibits pro-apoptotic proteins to protect dopaminergic neurons from oxidative stress	[7]
Parkinson's Disease (PD)	BIM	Bax/caspase-3 apoptotic pathway	Rescues dopaminergic neuron loss and improves motor function in 6-OHDA-induced mice	[54]
Neuronal Survival (PC12 Cells)	BIM	ERK1/2 signaling pathway (NGF induces miR-221)	Downregulates BIM to enhance neuronal survival	[55]
Valproic Acid-Resistant Epilepsy	HIF-1α	Inflammatory pathway (HIF-1α mediates M1 microglial polarization)	Inhibits HIF-1α to reduce M1 microglial polarization and alleviate seizure severity	[56]
Neuroinflammation (LPS-Induced)	IRF2	Interferon regulatory pathway	Propofol downregulates miR-221 to restore IRF2, inhibiting microglial activation	[57]
Digestive System				
Bovine Viral Diarrhea Virus (BVDV) Infection	ATG7	ATG7-LC3 autophagic pathway	Downregulates ATG7 to inhibit autophagy and reduce BVDV replication	[59]
Fulminant Liver Failure	PUMA	Bcl-2 family apoptotic pathway	Inhibits PUMA to reduce hepatocyte apoptosis and delay liver failure	[60]
Liver Regeneration (Post-Partial Hepatectomy)	Arnt	Cell cycle regulatory pathway	Downregulates target genes to promote hepatocyte S-phase entry and proliferation	[8]

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Hepatic Inflammation	TIMP-3	TNF-α-converting enzyme (TACE) regulatory pathway (TIMP-3 is an inhibitor of TACE)	Inhibits TIMP-3 to amplify pro-inflammatory signaling	[62]
Inflammatory Bowel Disease (DSS-Induced)	Maf, IL23R	Th17 cell differentiation pathway	Inhibits Maf and IL23R to restrict Th17 cell expansion and alleviate colitis	[63]
Respiratory System				
Pulmonary Arterial Hypertension (PAH)	AXIN2	Wnt/β-catenin pathway (AXIN2 is a negative regulator of the pathway)	Activates the pathway to promote PASMC proliferation and PAH progression	[66]
Severe Asthma (ASMC Hyperproliferation)	p21WAF1, p27kip1	ASMC proliferation	Specifically drives airway smooth muscle cell hyperproliferation	[68]
LPS-Induced Acute Lung Injury (ALI)	SOCS1	NF-κB pathway (SOCS1 is a negative regulator of NF-κB)	Inhibits SOCS1 to exacerbate inflammation; miR-221 inhibition restores SOCS1 to alleviate ALI	[69]
Adipose and Endocrine Systems				
Obesity (Lipid Metabolism)	AdipoR1 (co-regulated with PTB)	Adiponectin signaling pathway	Downregulates AdipoR1 to impair adiponectin signaling and insulin sensitivity	[70]
Obesity (Lipid Metabolism)	ANGPTL8	Triglyceride storage regulatory pathway	Inhibits ANGPTL8 to reduce triglyceride storage in adipocytes	[71]
Mammary Epithelial Cells (Lactation)	FASN	Fatty acid synthesis pathway	Downregulates FASN to inhibit lipid synthesis; hormones downregulate miR-221 to promote lactation	[72]
Diabetes (Wound Healing)	THBS1	Angiogenic pathway (THBS1 is an anti-angiogenic factor)	Inhibits THBS1 to reduce keratinocyte apoptosis and promote wound closure	[75]
Diabetes (Inflammatory Regulation)	DYRK1A	STAT3 signaling pathway (DYRK1A mediates STAT3 phosphorylation)	Inhibits DYRK1A to reduce STAT3 phosphorylation and pro-inflammatory cytokine release	[76]

9. Future Directions and Challenges

Despite progress, three key challenges remain. First, the molecular basis for miR-221's context-dependent function needs clarification—for example, why it promotes the invasion of breast cancer but inhibits that of meningioma [11,12]. Integrative studies combining single-cell sequencing and proteomics may identify cell-specific co-regulators (e.g., lncRNAs, RNA-binding proteins) that modulate miR-221's target specificity. Second, miR-221's biomarker utility requires validation in

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large, diverse cohorts; for instance, serum miR-221-3p as a promising marker for papillary thyroid carcinoma [14], but its performance in multi-ethnic populations remains untested. Third, therapeutic delivery systems must be optimized: current strategies (e.g., antagomiRs, EV-based delivery [43]) lack cell specificity, which could limit efficacy and increase toxicity.

In summary, miR-221 represents a versatile target for disease diagnosis, prognosis, and treatment. By resolving context-dependent mechanisms and advancing translational studies, miR-221 potentially transits from preclinical research to clinical practice, benefiting patients with cancer, CVDs, and other miR-221-associated disorders.

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