Advances in the biological functions of miR-205 in various diseases (Review)

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Abstract. MicroRNAs (miRNAs/miRs) are critical post-transcriptional regulators of gene expression. Aberrant miRNA expression has been closely linked to the initiation and progression of a wide range of malignant and non-malignant disorders, prompting extensive investigation into their biological functions, regulatory mechanisms and clinical relevance. Among these molecules, miR-205 has attracted considerable attention owing to its unique expression patterns and context-dependent roles. Notably, miR-205 participates in epigenetic regulation, functions as either a tumor suppressor or oncogene, contributes to therapeutic resistance and exerts important effects on non-cancerous diseases. The present review provides a comprehensive overview of the current understanding of miR-205 in both malignant and non-malignant conditions, highlights its major target genes and associated signaling pathways, and discusses its potential utility in the development of precise diagnostic, prognostic and therapeutic strategies.

Contents

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1. Introduction

Cancer remains one of the most notable public health challenges worldwide. Although the global disease burden persists, overall cancer-related mortality has declined in recent decades, largely due to the widespread implementation of early screening programs, increased emphasis on preventive strategies and the continuous development of innovative therapeutic modalities (1). Contemporary oncology has adopted a multidisciplinary and collaborative model of comprehensive care, integrating surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy. In clinical settings, combination chemotherapy continues to represent the standard first-line treatment for metastatic pancreatic cancer. Notably, fluorouracil-based combination regimens have demonstrated superior survival outcomes in patients with advanced pancreatic disease when compared with gemcitabine combined with taxane-based therapies (2). In addition, multidisciplinary team-guided preoperative interventions serve a pivotal role in optimizing perioperative management and improving outcomes for patients with gastrointestinal malignancies (3). Beyond conventional treatments, Traditional Chinese Medicine has been shown to exhibit diverse biological activities, including immunomodulatory, anti-inflammatory and direct antitumor effects, thereby providing promising options for adjunctive cancer therapy (4,5). In recent years, nanomedicine has emerged as a transformative approach in oncology, exploiting nanoscale size effects and tunable surface characteristics. Through mechanisms such as targeted drug delivery, controlled release and enhanced immunogenicity, nanoparticle-based systems can synergize with immunotherapy to improve therapeutic efficacy in malignancies such as prostate cancer. In addition, these platforms hold potential for overcoming immune evasion and reshaping the tumor microenvironment (6). Furthermore, advances in smart nanocarriers and stimulus-responsive drug delivery systems are accelerating the transition of cancer therapy toward greater precision and personalization. Nevertheless, conventional

therapeutic strategies continue to face substantial limitations, including treatment-related toxicity, radio- and chemoresistance, and pronounced heterogeneity in therapeutic efficacy across tumor types. For example, survival rates for pancreatic cancer and glioblastoma remain markedly lower than those observed in breast and prostate cancer (7). Consequently, the identification of novel therapeutic strategies capable of reversing drug resistance, enhancing treatment responsiveness and minimizing adverse effects remains a critical priority and a central focus of contemporary oncology research.

MicroRNAs (miRNAs/miRs) are endogenous, non-coding RNA molecules 20-24 nucleotides in length that function as critical post-transcriptional regulators of gene expression. Their principal mechanism involves binding to complementary sequences within the 3'-untranslated regions of target mRNAs, thereby inducing transcriptional repression or translational inhibition (8). Through this mode of regulation, miRNAs govern a wide spectrum of essential biological processes, including cell proliferation, differentiation, apoptosis and metabolic homeostasis. Notably, individual miRNAs are capable of targeting hundreds of genes and a single gene may be simultaneously regulated by multiple miRNAs, collectively forming highly complex and interconnected regulatory networks (9). This extensive regulatory capacity underscores the indispensable role of miRNAs in maintaining cellular equilibrium. Accordingly, aberrant miRNA expression has emerged as a defining feature of numerous pathological conditions, including malignant tumors (10), cardiovascular diseases (11), neurodegenerative disorders (12) and immune dysregulation (13). Advances in high-throughput sequencing technologies and bioinformatics analyses have further emphasized the clinical potential of miRNAs as diagnostic biomarkers and therapeutic targets, firmly establishing them as a central focus of epigenetic research (14,15). In oncology, miRNAs are increasingly recognized for their crucial involvement in maintaining cancer stem cell properties and modulating therapeutic responses, particularly in the development of drug resistance (16). Among these regulatory molecules, miR-205 exhibits highly context-dependent expression patterns and functional roles that vary substantially across different tissues and cancer types. Its ability to act either as an oncogene or as a tumor suppressor, a phenomenon commonly referred to as a 'dual role' in cancer biology, has attracted considerable scientific attention (17). Beyond oncogenesis, miR-205 also participates in a range of non-malignant pathological processes. The present review systematically summarizes advances in the understanding of miR-205, encompassing its biological characteristics, regulatory mechanisms, functional roles and prognostic importance across diverse diseases. Furthermore, it integrates current evidence on key target genes and signaling pathways associated with miR-205, thereby providing a foundation for the development of precise diagnostic tools and targeted therapeutic strategies.

2. Expression patterns and physiological functions of miR-205

Initially identified in mice and pufferfish, miR-205 is now recognized as an evolutionarily conserved miRNA, with homologs present across species ranging from zebrafish to humans (18,19). In humans, miR-205 is encoded on chromosome 1q32.2. As research has progressed, it has become evident that the biological functions of miR-205 in cancer are highly context-dependent. Whether miR-205 exerts oncogenic or tumor-suppressive effects is largely determined by the cellular microenvironment and the specific gene networks under its regulation (17). Similar to most miRNAs, miR-205 does not induce cellular phenotypic changes, such as alterations in proliferation, migration or invasion, through the modulation of a single target gene. Instead, it concurrently regulates multiple downstream targets, thereby initiating complex and interconnected signaling cascades. For example, in lung cancer models, downregulation of miR-205 results in the upregulation of the transcription factor zinc finger E-box binding homeobox (ZEB)2, which subsequently suppresses erbB3 expression. This multilayered regulatory axis ultimately enhances tumor cell proliferation and invasiveness, thereby accelerating disease progression. Notably, the reduction in erbB3 expression represents an indirect downstream consequence of miR-205 dysregulation in this context (20).

Beyond tumor biology, miR-205 serves an essential role in maintaining epithelial homeostasis, and regulating tissue repair and scar formation (Fig. 1). Loss of miR-205 disrupts PI3K/AKT signaling, leading to impaired proliferation, adhesion and migration of skin progenitor and stem cells. Such dysregulation can result in defective epidermal barrier formation, abnormal hair follicle morphogenesis, and, in severe cases, neonatal lethality (21). Supporting these observations, Jiang *et al* (22) employed Agilent miRNA microarrays combined with quantitative (q)PCR validation to demonstrate marked downregulation of miR-205 in hypertrophic scar tissue. Functional analyses revealed that miR-205 overexpression suppressed fibroblast migration, scar hyperplasia and collagen synthesis by directly targeting thrombospondin-1. Consistently, Qi *et al* (23) reported that miR-205 can inhibit extracellular matrix production through direct targeting of Smad2, thereby attenuating hypertrophic scar formation.

Emerging evidence has further indicated that miR-205 participates in regulatory crosstalk involving long non-coding RNAs (lncRNAs) and mRNAs via competition for shared miRNA response elements. In this competitive endogenous RNA (ceRNA) network, lncRNAs can function as molecular sponges for miRNAs, binding to their complementary sequences and relieving repression of miRNA target genes, thus adding an additional layer of post-transcriptional regulation (24). In the context of keloid formation, Su *et al* (25) demonstrated that the lncRNA HOXA11-AS may act as a ceRNA for miR-205. Silencing HOXA11-AS or restoring miR-205 expression significantly inhibited fibroblast proliferation and extracellular matrix deposition while promoting apoptosis, thereby suppressing pro-fibrotic processes. Notably, the functional consequences of miR-205 regulation are highly context-specific. In skin wound healing, Wang *et al* (26) reported that miR-205 downregulation facilitated keratinocyte migration and accelerated wound closure by suppressing integrin α5 expression. By contrast, Lin *et al* (27) observed a pro-healing role for miR-205 in the cornea, where its overexpression promoted epithelial repair by targeting the potassium channel KCNJ10 and enhancing cellular proliferation.

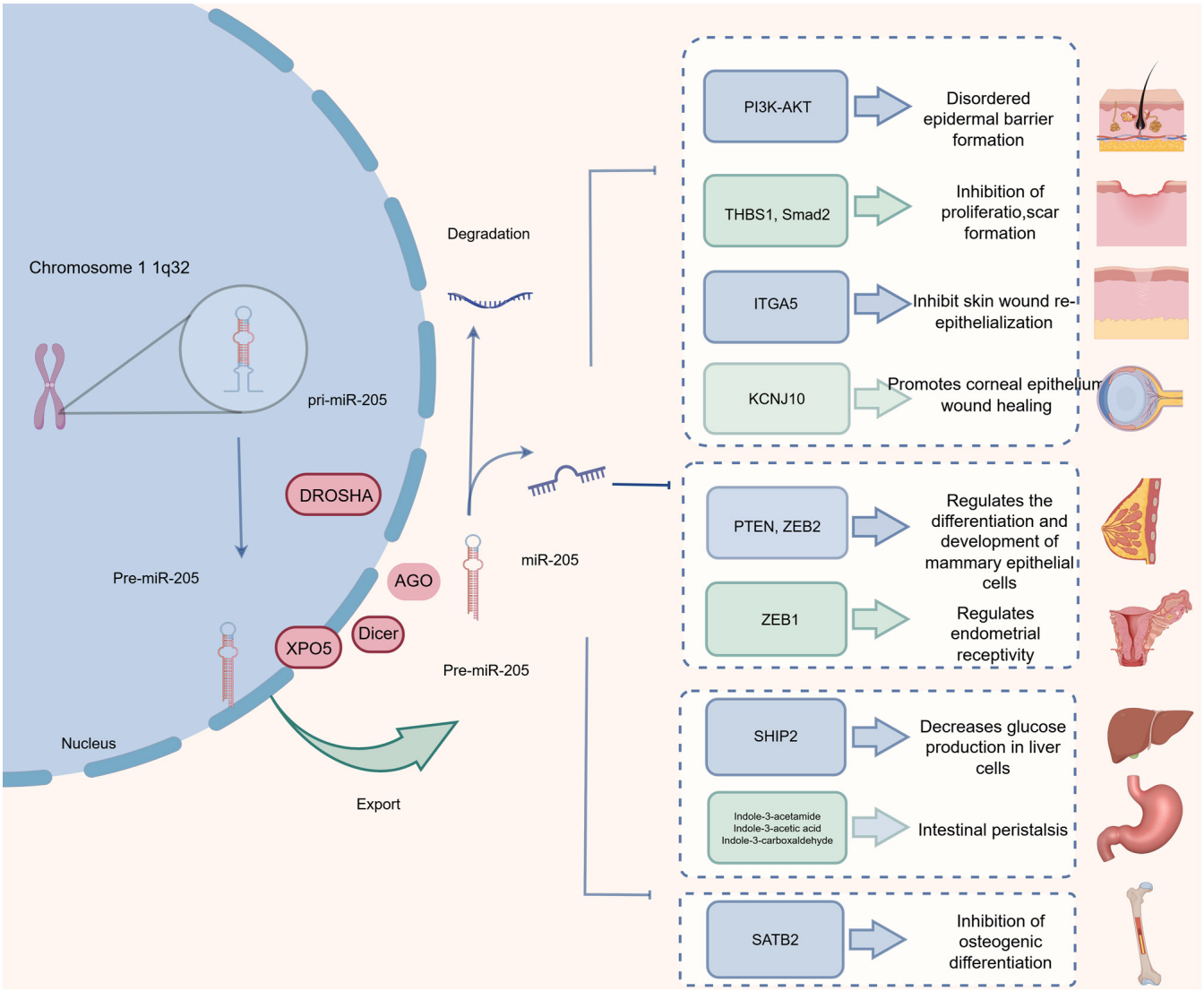

Figure 1. Expression and physiological function of miR-205 (normal arrows indicate promotion and T-shaped arrows indicate inhibition). miR, microRNA; DROSHA, drosha ribonuclease III; XPO5, exportin-5; DICER1, ribonuclease III gene; THBS1, thrombospondin 1 gene; SMAD2, SMAD family member 2; ITGA5, integrin, α5 (fibronectin receptor, alpha polypeptide); KCNJ10, potassium inwardly rectifying channel subfamily J member 10; SHIP2, Src homology 2 domain-containing inositol 5'-phosphatase 2; SATB2, special AT-rich sequence-binding protein 2.

In a normal mammary epithelial cell culture model, miR-205 was found to be highly expressed in progenitor-like cells, where it promoted mammary epithelial differentiation and development through repression of ZEB2 (28). Beyond epithelial tissues, miR-205 has also been implicated in reproductive biology. Yu *et al* (29) reported a marked upregulation of miR-205 in endometrial epithelial cells following ovulation, whereas reduced miR-205 expression was observed in the endometrial tissues of women with infertility. Notably, intrauterine administration of a miR-205 inhibitor during the mid-secretory phase, corresponding to the window of implantation, significantly decreased embryo implantation rates and was associated with altered regulation of ZEB1. These findings suggest a critical role for miR-205 in modulating endometrial receptivity and embryo implantation (29).

Beyond pathological conditions, miR-205 also serves as an important regulator of fundamental physiological processes, including systemic metabolism and cellular differentiation. Its role in metabolic regulation has been highlighted by two independent studies. In hepatocytes, miR-205 suppresses the SHIP2/FOXO signaling axis, thereby reducing hepatic glucose production (30). In parallel, emerging evidence has suggested that miR-205 enhances intestinal motility by modulating gut microbiota composition and tryptophan metabolism (31). In the context of cell differentiation, Hu *et al* (32) demonstrated that miR-205 overexpression significantly inhibited the osteogenic differentiation potential of bone marrow-derived mesenchymal stem cells (BMSCs). Mechanistically, this effect was mediated through direct targeting of the SATB2/Runx2 signaling pathway, as reflected by the downregulation of key osteogenic markers, including bone sialoprotein, osteopontin, alkaline phosphatase (ALP) and osteocalcin.

3. Transcriptional regulation of miR-205

Regulation by transcription factors. The transcriptional regulation of miR-205 is orchestrated by multiple transcription factors, among which p53 serves a central role (33). Specifically,

p53 directly activates miR-205 transcription by binding to a canonical p53 response element (p53RE) located within the upstream promoter region of the miR-205 gene. Through this regulatory axis, miR-205 contributes to the control of critical cellular processes, including cell cycle arrest, apoptosis and the maintenance of genomic stability. Consequently, loss-of-function mutations in TP53 can disrupt this transcriptional activation, representing a key mechanism underlying miR-205 downregulation in several malignancies, such as triple-negative breast cancer (BC) (34). In addition to p53, the closely related family members p63 and p73 also recognize and bind to p53REs owing to their structural homology with p53, thereby positively regulating miR-205 expression (35). However, in specific tumor microenvironmental contexts, mutant p53 has been shown to indirectly repress miR-205 transcription by destabilizing p63 and impairing its transcriptional activity (36). Other transcription factors further contribute to the fine-tuned regulation of miR-205. The transcription factor Sp1 can bind to regulatory regions upstream of the miR-205 host gene under conditions of DNA damage, thereby promoting the co-transcription of miR-205 and its host gene. By contrast, the epithelial-mesenchymal transition (EMT)-associated transcription factor Twist1 directly interacts with the miR-205 promoter to suppress its transcription, linking miR-205 regulation to EMT and tumor progression pathways (37).

Epigenetic regulation. DNA methylation is a fundamental epigenetic modification characterized by the addition of a methyl group to the fifth carbon of cytosine residues, resulting in the formation of 5-methylcytosine. Genomic regions enriched in cytosine-guanine dinucleotides, known as CpG islands, are typically located within upstream regulatory elements, particularly gene promoter regions. Aberrant hypermethylation of promoter-associated CpG islands in tumor suppressor genes can lead to transcriptional silencing and functional inactivation, representing a common and critical mechanism driving cancer initiation and progression (38). Epigenetic modifications, including DNA and histone methylation, serve pivotal roles in a wide range of pathophysiological processes, such as oncogenesis and aging, by regulating gene expression, modulating chromatin architecture, influencing protein function and affecting RNA processing. Among these mechanisms, DNA methylation is essential for maintaining genomic stability, organizing higher-order chromatin structure and precisely controlling transcriptional activity (39).

Accumulating evidence has indicated that the expression of specific miRNAs, including miR-205, is frequently regulated by aberrant DNA methylation during disease development, particularly in cancer, where CpG island hypermethylation commonly leads to the silencing of tumor-associated miRNAs (40). For miR-205, CpG sites are densely distributed within both the promoter region of its host gene (MIR205HG) and the miRNA coding locus itself (34). In HER2-positive BC, activation of the HER2/Ras/Raf/MEK/ERK signaling cascade induces the upregulation of DNA methyltransferases, resulting in hypermethylation of the MIR205HG promoter and consequent transcriptional repression of miR-205 (41). This epigenetic silencing contributes to BC progression, as reduced miR-205 expression is associated with the enhanced proliferation, invasion and migratory capacity of cancer cells. Thus, elucidating the methylation-dependent regulation of miR-205 not only expands the understanding of miRNA-mediated oncogenic signaling in BC but also highlights potential avenues for epigenetically targeted therapeutic intervention.

Supporting this regulatory paradigm, Mancini *et al* (42) reported coordinated histone modifications at the miR-205 locus in prostate cancer cells, including increased levels of the repressive mark H3K27me3 and reduced enrichment of the activating mark H3K4me3. Together, these chromatin alterations may synergize with DNA methylation to enforce stable silencing of miR-205 (42). Similarly, epigenetic mechanisms have been implicated in EMT during lung cancer progression. Tellez *et al* (43) demonstrated that EMT initiation was preceded by chromatin remodeling characterized by H3K27me3 accumulation, which was subsequently consolidated by DNA methylation, leading to permanent repression of miR-200b, miR-200c and miR-205. Downregulation of these miRNAs has been shown to be strongly associated with a dedifferentiated phenotype in both immortalized human bronchial epithelial cells and primary lung tumors.

Beyond oncology, aberrant methylation of the miR-205 promoter has also been observed in non-malignant disorders. In a cellular model of Parkinson's disease (PD), Wang *et al* (44) identified hypermethylation of the miR-205 promoter region. Notably, pharmacological demethylation restored miR-205 expression and suppressed leucine-rich repeat kinase 2 (LRRK2), implicating miR-205 methylation as a critical regulatory mechanism in PD pathogenesis and a potential therapeutic target (44). Moreover, emerging evidence has suggested that epigenetic regulation of miR-205 may influence immune-related disease outcomes. In the context of COVID-19, Vaz *et al* (45) reported that elevated circulating miR-205 levels at hospital admission were associated with an increased risk of adverse clinical outcomes, proposing peripheral blood miR-205 as a potential prognostic biomarker for predicting progression to severe or critical disease. Collectively, these findings underscore the central role of epigenetic dysregulation of miR-205 across a broad spectrum of pathological conditions, and highlight its considerable promise as both a prognostic indicator and a target for epigenetically informed therapeutic strategies.

4. Role in non-cancerous diseases

Cardiovascular diseases. The role of miR-205 in cardiovascular and hypertensive disorders is multifaceted and highly context-dependent, with evidence supporting both protective and disease-modifying functions. In the setting of environmental stress-induced cardiotoxicity, Feng *et al* (46) demonstrated that PM2.5 exposure-mediated upregulation of miR-205 attenuated myocardial injury by targeting IL-1 receptor-associated kinase-like 2 and activating the TNF receptor-associated factor 6/NF-κB signaling pathway. Consistent with these cardioprotective effects, Xiao *et al* (47) reported that enhanced miR-205 expression in atrial myocytes from an atrial fibrosis rat model markedly suppressed atrial fibroblast proliferation and migration through downregulation of fibrosis-associated markers, including collagen I, α-smooth muscle actin (α-SMA) and prolyl 4-hydroxylase subunit α3. A similar protective role of miR-205 has been observed in

hypertensive disorders of pregnancy. Liu *et al* (48) showed that IL-32-mediated downregulation of miR-205 promoted trophoblast invasiveness via activation of the MMP2/MMP9/NF-κB axis, suggesting that elevated miR-205 expression may suppress disease initiation and progression in pregnancy-induced hypertension. The protective effects of miR-205 extend to multiple cardiovascular pathologies through distinct molecular mechanisms. In vascular disease, Huang *et al* (49) demonstrated that the natural compound icariin alleviated atherosclerosis by upregulating miR-205, thereby inhibiting ERBB4 signaling in vascular smooth muscle cells. By contrast, homocysteine (Hcy)-induced pulmonary vascular dysfunction has been linked to hypermethylation-mediated silencing of miR-205. Under physiological conditions, miR-205 supports microvascular angiogenesis by targeting FOXO1; thus, its epigenetic repression contributes to vascular impairment (50). In the context of cardiac fibrosis, Xiao *et al* demonstrated that miR-205 overexpression can directly target euchromatic histone lysine methyltransferase 2, thereby attenuating atrial fibrosis, and improving associated mitochondrial and metabolic dysfunctions (51).

Diabetes. Accumulating evidence has indicated that miR-205 serves diverse and context-dependent roles in the pathogenesis of diabetic complications. In the setting of diabetic wound healing, Liu *et al* (52) treated human umbilical vein endothelial cells with diabetic foot ulcer-derived extracellular vesicles (DF-EVs; 5 μg/ml) and control vesicles. Functional assays revealed that DF-EV exposure markedly impaired endothelial cell migration and angiogenic capacity. Consistently, wounds treated with DF-EVs exhibited markedly reduced neovascularization within local granulation tissue by day 7, indicating that DF-EVs negatively regulated angiogenesis in diabetic foot ulcers. Mechanistically, miR-205 was found to be enriched in EVs isolated from diabetic wound fluid, where it inhibited angiogenesis and delayed wound healing by suppressing vascular endothelial growth factor A (VEGFA) at both the mRNA and protein levels (52,53). By contrast, miR-205 has been implicated in the progression of diabetic nephropathy through a distinct regulatory mechanism. Zheng *et al* (54) identified a double-negative feedback loop in which miR-205 directly targeted histone deacetylase (HDAC)2, whereas HDAC2 reciprocally repressed miR-205 transcription via specificity protein 1 (SP1) binding sites. This HDAC2/SP1/miR-205 regulatory circuit can promote extracellular matrix accumulation in renal tubular epithelial cells, thereby accelerating the progression of diabetic nephropathy (54). Beyond vascular and renal complications, miR-205 also contributes to pancreatic islet dysfunction. Ouni *et al* (55) reported notable upregulation of miR-205 in the pancreatic islets of diabetes-prone mice, where it impaired islet function by directly targeting the diabetes-associated transcription factor Tcf7l2.

Neurological diseases. Beyond its established roles in cancer and metabolism, miR-205 is increasingly recognized as a critical regulator in diverse neurological disorders. In PD, a neurodegenerative condition marked by progressive motor dysfunction, Wang *et al* (44) demonstrated that hypermethylation-induced silencing of the miR-205 promoter contributed to disease pathogenesis via dysregulation of LRRK2 expression. In models of depression, He *et al* (56) reported that Mahonia alkaloids ameliorated depressive-like behaviors by downregulating miR-205, which led to increased expression of key neuroprotective factors such as connexin 43, brain-derived neurotrophic factor and cAMP response element-binding protein. Furthermore, neurotoxicity induced by sevoflurane (Sev), a commonly used volatile anesthetic, can be mitigated through modulation of miR-205 (57,58). Zhang *et al* (58) reported that knockdown of the lncRNA NKILA alleviated Sev-induced neurotoxicity by downregulating miR-205 and subsequently upregulating ELAVL1. Furthermore, in cerebral ischemia models, Yang *et al* (59) demonstrated that dexmedetomidine treatment upregulated miR-205, which inhibited high-mobility group box 1 (HMGB1), thereby reducing oxidative stress and inflammation, and improving ischemia/reperfusion injury outcomes in rats.

Rheumatoid arthritis (RA), osteoporosis (OP) and other orthopedic diseases. miR-205 exhibits dynamic expression during the chondrogenic differentiation of BMSCs and serves important roles in multiple orthopedic diseases, including RA and OP (60). Ma *et al* (61) demonstrated that exosomal miR-205 (exo-miR-205) derived from BMSCs attenuated RA progression *in vitro* by targeting MDM2, which in turn modulated the MAPK and NF-κB signaling pathways, key mediators of inflammation and joint degradation. In OP, Huang *et al* (60) identified miR-205 as upregulated via microarray and bioinformatics analyses, findings subsequently validated by reverse transcription (RT)-qPCR in clinical samples from 30 patients with OP. Functional studies revealed that miR-205 expression was reduced during osteogenic differentiation, and its overexpression inhibited this process by targeting RUNX2, resulting in reduced expression of osteogenic markers such as collagen type I α1 and ALP. Conversely, inhibition of miR-205 promoted osteogenic differentiation (60). In intervertebral disc degeneration (IDD), Zhu *et al* (62) reported that the lncRNA LINC00284 was upregulated in degenerative disc tissues and IL-1β-stimulated nucleus pulposus (NP) cells. Knockdown of LINC00284 mitigated NP cell degeneration and extracellular matrix degradation by functioning as a molecular sponge for miR-205, thereby relieving suppression of the Wnt/β-catenin pathway. This led to enhanced cell proliferation, reduced apoptosis and decreased MMP3 expression, ultimately alleviating IDD progression (62).

Chronic periodontitis. Jiang *et al* (63) identified a potential role for miR-205 in the resolution of chronic periodontitis. This previous study detected elevated serum levels of miR-205 in patients following treatment, which were associated with downregulation of its target, HMGB1. Clinically, increased miR-205 expression was associated with improvements in key periodontal parameters, including probing depth, attachment loss, plaque index and gingival index, whereas HMGB1 expression was positively associated with disease severity. These findings position miR-205 and HMGB1 as critical modulators of chronic periodontitis pathogenesis and as promising therapeutic targets (63). Building on the recognized importance of the T helper cell (Th)17/regulator T cell (Treg) balance in inflammatory regulation (64), Kang *et al* (65) explored the therapeutic potential of exo-miR-205 derived

from periodontal ligament stem cells. In a rat model of periodontitis, administration of exo-miR-205 targeted X-box binding protein 1, shifted immune homeostasis towards Tregs, attenuated pro-inflammatory cytokine production, including TNF-α, IL-6 and IL-1β, and ultimately suppressed disease progression (65).

Allergic rhinitis (AR). AR is an immunoglobulin E (IgE)-mediated inflammatory disorder of the upper airways. Clinical analysis by Suojalehto *et al* (66) detected upregulation of miR-205 in the nasal mucosa of patients with symptomatic AR. Complementary experimental data from Zhang *et al* (67) using an ovalbumin (OVA)-sensitized murine model of AR showed notable increases in miR-205 expression. Mechanistically, knockdown of miR-205 ameliorated allergic responses by reducing serum levels of total and OVA-specific IgE, suppressing local production of Th2 cytokines (IL-4, IL-5 and IL-13) in the nasal mucosa, thereby inhibiting AR development (67). In a related study, the circular RNA (circRNA) circARF3 has been shown to alleviate AR symptoms in mice by acting as a molecular sponge for miR-205, resulting in upregulation of Sirtuin 5 and consequent attenuation of allergic inflammation (68). Collectively, these findings underscore a pathogenic role for miR-205 in AR and highlight its potential as a therapeutic target.

Other inflammatory conditions. The role of miR-205 in inflammation is highly context-dependent, exhibiting both pathogenic and protective effects depending on the disease model. In abdominal aortic aneurysm (AAA), Kim *et al* (69) identified a pathogenic role for miR-205, which can target the protective factors TIMP3 and RECK. This targeting led to unchecked MMP activity and exacerbated inflammation, thereby driving AAA progression. Conversely, in models of sepsis and post-traumatic lung injury, miR-205 exerts a protective effect by targeting HMGB1, mitigating excessive inflammatory responses and reducing tissue damage (70).

Respiratory diseases. In respiratory diseases, miR-205 serves diverse roles through the regulation of distinct molecular targets. Zhao *et al* (71) demonstrated that under hypoxic conditions, proline-rich protein VII induced the upregulation of miR-205 in rat pulmonary vascular smooth muscle cells. Elevated miR-205 attenuated pulmonary hypertension by targeting β-catenin, leading to inhibition of cell proliferation and promotion of apoptosis (70). In acute respiratory distress syndrome (ARDS), the serum levels of miR-205 were shown to be elevated and to exert protective effects by targeting COMM domain-containing protein 1. This interaction antagonizes the pro-survival function of the lncRNA SNHG5 in A549 cells, thereby attenuating ARDS pathogenesis (72). In pulmonary fibrosis (PF), Sun *et al* (73) demonstrated that miR-205 overexpression improved fibrotic pathology by targeting GATA-binding protein 3 and suppressing endoplasmic reticulum stress in a murine model. Similarly, in silicosis, miR-205 expression has been reported to be downregulated in alveolar macrophages. Mechanistic experiments have revealed that miR-205 targets E2F1 to reduce S-phase kinase-associated protein 2-mediated ubiquitination of Beclin1, promoting autophagy and inhibiting the progression of silicosis-associated PF (74).

Urinary system disorders. Renal interstitial fibrosis (RIF), a progressive and irreversible pathological hallmark of chronic kidney disease, ultimately leads to end-stage renal disease. In a unilateral ureteral obstruction mouse model of RIF, miR-205 expression has been shown to be markedly downregulated. By contrast, restoration of miR-205 levels suppresses the progression of fibrosis by inhibiting HDAC5, resulting in reduced expression of key fibrotic markers, including α-SMA, collagen IV and fibronectin (75). In acute kidney injury, Zhang *et al* (76) demonstrated that miR-205 overexpression ameliorated sepsis-induced renal damage in rats by concurrently targeting HMGB1 and phosphatase and tensin homolog (PTEN). Furthermore, Zhou *et al* (77) identified a novel regulatory axis in sepsis-associated acute kidney injury (SA-AKI), wherein the circRNA circ_0006944, upregulated in patients with SA-AKI, acted as a molecular sponge for miR-205. Functional upregulation of miR-205 alleviated SA-AKI by targeting ubiquitin-like protein 4A (UBL4A), highlighting the circ_0006944/miR-205/UBL4A pathway as a key mechanism in this condition.

Psoriasis. In psoriasis, Xue *et al* (78) observed notable downregulation of miR-205 in patient skin lesions. Functional assays showed that miR-205 overexpression ameliorated the psoriatic phenotype in a mouse model by targeting angiopoietin-2, VEGFA, bone morphogenetic protein and activin membrane-bound inhibitor, thereby inactivating the MAPK and Wnt/β-catenin signaling pathways (78).

Digestive system diseases. The role of miR-205 in liver injury is complex and context-dependent. In trichloroethylene (TCE)-induced liver injury, Wang *et al* (79) reported that miR-205 overexpression exacerbated hepatic damage by targeting retinoic acid receptor-related orphan receptor α (RORα), promoting M1 macrophage polarization and inflammation. Similarly, Hu *et al* (80) revealed that miR-205 was upregulated in non-alcoholic fatty liver disease models and contributed to disease progression by targeting neuraminidase 1. Conversely, Fang *et al* (81) revealed a protective role in alcohol-related liver disease, where miR-205 targeted importin α5 to suppress NF-κB pathway activation and mitigate liver pathology. Beyond hepatic diseases, Smith *et al* (82) identified downregulation of miR-205 in ulcerative esophagitis. This previous functional study indicated that miR-205 upregulation may promote epithelial repair in response to reflux injury by inhibiting cytokeratin 14 expression, inducing apoptosis and suppressing proliferation in esophageal epithelial cells (82).

Influenza A. Bao *et al* (83) confirmed that both oseltamivir and Jin Chai Kangbingdu Capsule can inhibit influenza A virus replication by upregulating miR-205, which directly targets the viral nucleoprotein gene and suppresses its expression.

Sepsis. In a septic model using lipopolysaccharide-induced HK-2 cells, the lncRNA TapSAKI has been reported to be upregulated, whereas miR-205 is downregulated.

Mechanistically, miR-205 overexpression can alleviate cytotoxic injury and suppress sepsis progression by targeting interferon regulatory factor 3 (84).

Myelodysplastic syndrome (MDS). Jang *et al* (85) identified a marked 12.5-fold increase in serum miR-205 levels in 65 patients with MDS compared with in 11 controls. Subsequent validation demonstrated that miR-205 promoted MDS pathogenesis by targeting the tumor suppressor PTEN (85).

It is evident that miR-205 serves a crucial role in various non-malignant diseases, holding profound implications for the treatment of diverse conditions (Fig. 2).

5. Role of miR-205 in malignant tumors

Expression characteristics in cancer. miR-205 exhibits distinct, tissue-specific expression patterns across various malignancies, which underlie its context-dependent dual role in tumorigenesis and cancer progression (86). It can function either as a tumor suppressor, commonly downregulated in cancers such as renal cell carcinoma (87), prostate cancer (88), BC, colorectal cancer (CRC) and melanoma (89), or as an oncogene, promoting tumor development in malignancies including non-small cell lung cancer (NSCLC) (90), bladder cancer (91), ovarian cancer (92), nasopharyngeal carcinoma (NPC), head and neck cancer (93) and esophageal adenocarcinoma (94). This functional dichotomy highlights the complex, microenvironment-dependent regulatory networks that govern miR-205 activity (Table I) (17,93,95-112).

Tumor suppressive role. Evidence suggests that the loss of miR-205 expression may facilitate mammary gland development (95). Consistent with its tumor-suppressive role, miR-205 is frequently downregulated in BC, with expression levels inversely associated with malignancy grade (96). Functionally, Kalinkova *et al* (97) demonstrated that restoring miR-205 expression in BC cells inhibited invasion and migration by targeting ZEB1. This anti-invasive effect has been further supported by findings that miR-205 upregulation promotes the epithelial marker E-cadherin while suppressing the mesenchymal marker vimentin (98). The tumor-suppressive role of miR-205 extends beyond BC. For example, in gastric cancer, Ma *et al* (99) reported that miR-205 impeded cell proliferation and invasion by downregulating CXCL11 and inhibiting AKT signaling. Similarly, Wang *et al* (100) reported that miR-205 can target cyclin B2 to inhibit proliferation and migration in thyroid cancer cells, where Wang *et al* (101) demonstrated that suppression of the PTEN/AKT pathway by miR-205 curbed malignant phenotypes in renal cell carcinoma.

The function of miR-205 shows notable context dependence, even within the same cancer type. In ovarian cancer, some studies have described a tumor-suppressive role: miR-205 expression has been reported to be downregulated in ovarian cancer cells, with its overexpression inhibiting proliferation and migration by targeting MAPK10 (102). Conversely, Cai *et al* (103) reported an oncogenic function, showing that miR-205 enhanced invasion in ovarian cancer cell lines (OVCAR-5, OVCAR-8 and SKOV-3) and promoted tumorigenesis by downregulating TCF21, which led to upregulation of MMP2 and MMP10 (92,103). This suggests that the role of miR-205 may vary across different molecular subtypes or stages of ovarian cancer. Similarly, in pancreatic ductal adenocarcinoma (PDAC), evidence points to a dual role: Wang *et al* (104) identified elevated miR-205 in plasma-derived EVs and PDAC tissues, whereas EV-miR-205 appeared to suppress metastasis by targeting VEGFA and was negatively associated with lymph node metastasis.

Oncogenic role. miR-205 acts as an oncogene in several malignancies, as demonstrated by its upregulated expression in both tumor tissue and patient serum. In cervical cancer, miR-205 overexpression has been shown to promote proliferation, invasion and migration by directly targeting and downregulating chimerin 1 (105-108). Similarly, in NPC, miR-205 enhances tumorigenesis and progression through multiple mechanisms: It drives cell proliferation and invasion by suppressing calmodulin-1 (109), and facilitates metastasis via exosome-mediated downregulation of desmocollin-2, which activates the EGFR/ERK pathway and upregulates MMP2 and MMP9 (110). This oncogenic role is also evident in liver cancer, where miR-205 targets DNAJA1 to promote proliferation and metastasis (111), and in NSCLC, where it fosters tumor progression by downregulating APBB2 (112). The functional importance of miR-205 in these types of cancer is further emphasized by regulatory interactions with tumor-suppressive lncRNAs such as VENTXP1, which inhibits head and neck squamous cell carcinoma tumorigenesis by repressing miR-205 and consequently upregulating its target ankyrin repeat domain 2 (93).

6. Clinical application prospects

Diagnostic value. miRNAs are highly stable molecules that can be reliably detected in various physiological fluids, such as serum and plasma, as well as tissue specimens, using multiple robust technical platforms (113). Due to their notable potential for elucidating disease mechanisms, and advancing diagnostic and therapeutic strategies, miRNAs have become a major focus of biomedical research (114). Notably, their application as non-invasive biomarkers for cancer diagnosis and prognosis has garnered substantial interest (115).

Evidence supports the substantial diagnostic and prognostic value of miR-205 in several types of cancer. Re *et al* (116) conducted a miRNome analysis using next-generation sequencing on 43 patients with intestinal-type sinonasal adenocarcinoma (ITAC) following surgical resection. This previous study revealed downregulation of miR-205 in tumor tissues, with low miR-205 expression serving as an independent predictor of poorer disease-free survival (DFS) and overall survival (OS), highlighting its potential as a prognostic biomarker for ITAC (116). Complementing these findings, Li *et al* (117) performed a meta-analysis evaluating the diagnostic efficacy of miR-205 in lung cancer, primarily squamous cell carcinoma, involving 564 patients and 667 controls. The analysis demonstrated high diagnostic performance, with a sensitivity of 0.88 (95% CI: 0.78-0.94), specificity of 0.78 (95% CI: 0.66-0.86) and an area under the receiver operating characteristic curve (AUC) of 0.90 (95% CI: 0.87-0.92). The diagnostic odds ratio of 25.86 further underscored its strong potential for lung cancer screening and

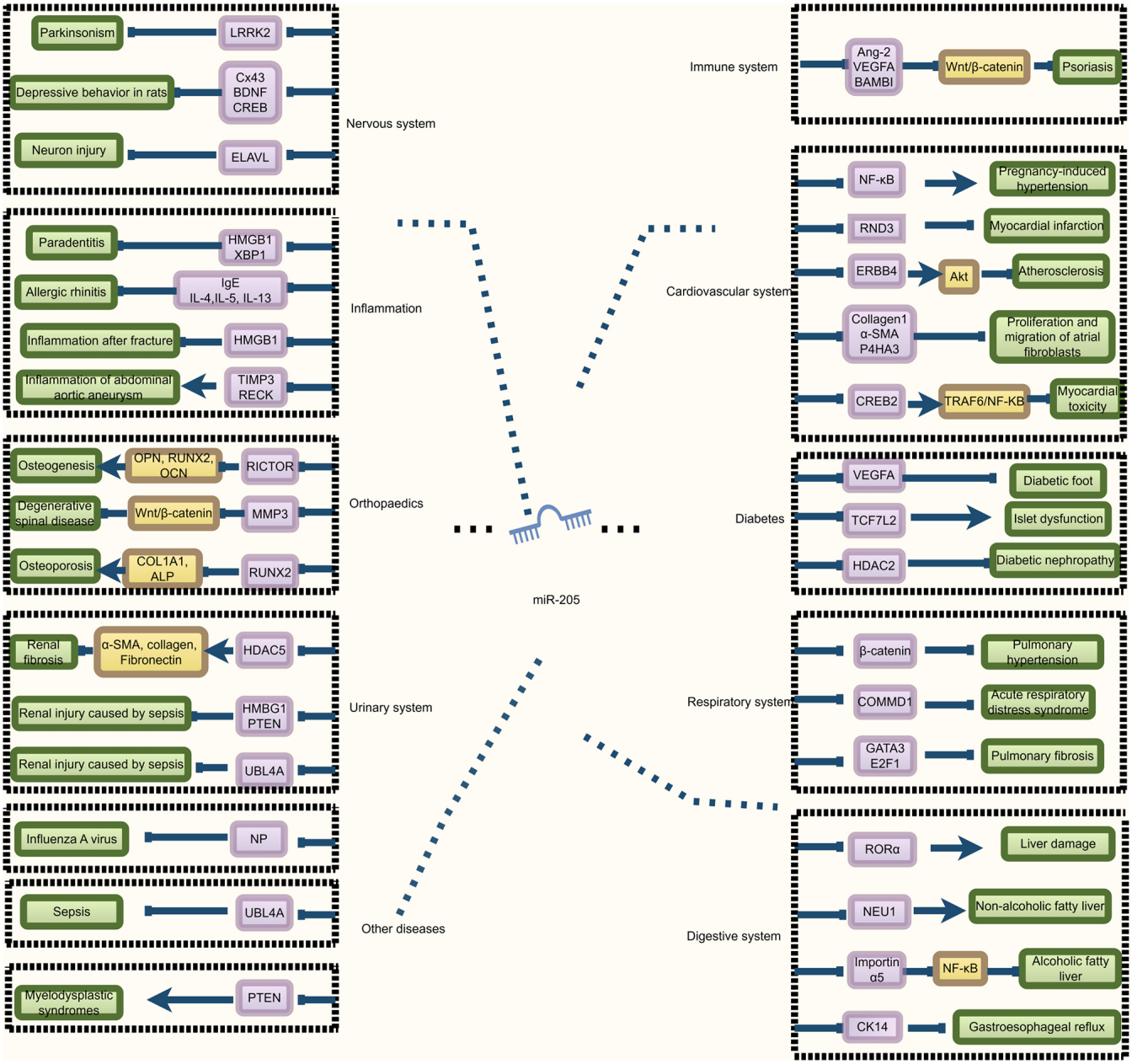

Figure 2. Role of miR-205 in non-cancerous diseases (normal arrows indicate promotion and T-shaped arrows indicate inhibition. MiR-205 regulates diseases (green) by inhibiting the downstream target gene (purple). LRKK2, leucine-rich repeat kinase 2; Cx43, connexin 43; BDNF, brain-derived neurotrophic factor; CREB, cAMP-response element binding protein; ELVAL, embryonic lethal abnormal vision like 1; HMGB1, high mobility group box 1; XBP1, X-box binding protein 1; IL, interleukin; TIMP3, TIMP metallopeptidase inhibitor 3; RECK, reversion-inducing cysteine-rich protein with Kazal motifs; RICTOR, RPTOR independent companion of MTOR complex 2; MMP3, matrix metalloproteinase 3; RUNX2, recombinant human Runt-related transcription factor 2; HDAC5, histone deacetylase 5; UBL4A, ubiquitin-like 4A; OPN, osteopontin; OCN, bone gamma-carboxyglutamate protein; ALP, alkaline phosphatase; α-SMA, α-smooth muscle actin; Ang-2, angiopoietin-2; BAMBI, BMP and activin membrane bound inhibitor; RND3, Rho family GTPase 3; ERBB4, Erb-B2 receptor tyrosine kinase 4; P4HA3, prolyl 4-hydroxylase subunit α3; CREB2, cyclic AMP-responsive element-binding protein 2; TCF7L2, transcription factor 7 Like 2; HDAC2, histone deacetylase 2; COMMD1, copper metabolism MURR1 domain 1; GATA3, GATA binding protein 3; E2F1, E2F transcription factor 1; RORα, RAR-related orphan receptor α; NEU1, neuraminidase 1; CK14, cytokeratin 14; TRAF6, TNF receptor-associated factor 6.

clinical application (117). The diagnostic utility of miR-205 is also supported by its detectability in circulating exosomes and EVs. Zhao *et al* (118), analyzing data from The Cancer Genome Atlas, reported notable downregulation of exo-miR-205 in patients with CRC, including those with early-stage disease. Although sensitivity (53.6%) and specificity (71.9%) for early-stage CRC were moderate, the notable postoperative increase in miR-205 levels suggested its potential as a dynamic marker for disease monitoring (118). This aligns with growing interest in EV-derived miRNAs as biomarkers for cancer diagnosis and prognosis (119). Supporting this, a clinical study by Bang *et al* (120) involving 220 subjects found that EV-derived miR-205 was elevated in patients with cancer-associated stroke compared with those with cancer alone, indicating its utility in predicting cancer-related coagulopathies. Similarly, Wang *et al* (121) demonstrated markedly elevated serum exo-miR-205 levels in patients with NSCLC relative to controls, further reinforcing its diagnostic relevance.

Table I. Roles of microRNA-205 in malignant tumor.

A, Tumor suppressive role

First author, year	Target gene	Cancer type	Mechanism	(Refs.)
Kalinkova *et al*, 2021	ZEB1	Breast cancer	Restrains invasion and migration	(97)
Shen *et al*, 2021	E-cadherin	Breast cancer	Restrains invasion and migration	(98)
Ma *et al*, 2021	CXCL11	Gastric cancer	Inhibition of proliferation and invasion	(99)
Wang *et al*, 2010	CCNB2	Thyroid cancer	Inhibition of proliferation and migration	(100)
Wang *et al*, 2016	PTEN	Renal carcinoma	Inhibition of proliferation, invasion and migration	(101)
Qiao *et al*, 2010	MAPK10	Ovarian cancer	Inhibition of proliferation and migration	(102)
Wang *et al*, 2025	VEGFA	Pancreatic ductal carcinoma	Inhibition of lymph node metastasis	(104)

B, Oncogenic role

First author, year	Target gene	Cancer type	Mechanism	(Refs.)
Zhang *et al*, 2020	ANKRD2	Head and neck squamous cell carcinoma	Ability to promote proliferation, invasion and migration	(93)
Ma *et al*, 2014; Xie *et al*, 2012; Witten *et al*, 2010 Liu *et al*, 2020	CHN1	Cervical cancer	Promotes proliferation, invasion and migration	(105-108)
Yang *et al*, 2022	DSC2	Nasal pharyngeal cancer	Promotes proliferation, invasion and migration	(110)
Guo *et al*, 2025	CALM1	Nasal pharyngeal cancer	Promotes proliferation, invasion and migration	(109)
Yi *et al*, 2022	DNAJA1	Liver cancer	Ability to promote proliferation and migration	(111)
Xu *et al*, 2021	APBB2	Non-small cell lung cancer	Ability to promote proliferation and migration	(112)

ZEB1, zinc finger E-box binding homeobox; CXCL11, C-X-C motif chemokine ligand 11; CCNB2, cyclin B2; PTEN, phosphatase and tensin homolog; MAPK10, mitogen-activated protein kinases; VEGFA, vascular endothelial growth factor A; ANKRD2, ankyrin repeat domain 2; CHN1, chimerin 1; DSC2, desmocollin-2; CALM1, calmodulin-1; DNAJA1, DnaJ heat shock protein family (Hsp40) member A1; APBB2, amyloid beta precursor protein binding family B member 2.

Zhao *et al* (122) investigated the diagnostic potential of miR-205 in thyroid nodules by analyzing patient serum samples. This previous study revealed that both miR-205 and thyroid stimulating hormone receptor (TSHR) mRNA expression levels were notably elevated in patients with benign or malignant thyroid nodules compared with those in the controls. For diagnosing thyroid nodules (vs. controls), miR-205 alone yielded an AUC of 0.867, outperforming TSHR mRNA (AUC=0.760). Notably, combining both markers improved diagnostic accuracy, achieving an AUC of 0.896 with a sensitivity of 96.43% and specificity of 76.81% at the optimal cut-off. Additionally, miR-205 and TSHR mRNA maintained moderate diagnostic efficacy in distinguishing malignant from benign nodules, with AUC values of 0.738 and 0.729, respectively. These findings collectively underscored the clinical utility of miR-205, especially when combined with TSHR mRNA, as a valuable biomarker panel for thyroid nodule diagnosis and risk stratification (122).

Prognostic value. miR-205 serves a pivotal regulatory role in gynecological malignancies and demonstrates prognostic potential across various types of cancer. A comprehensive meta-analysis by Wu *et al* (123), encompassing data from 5,835 patients, revealed that the prognostic impact of miR-205 was highly cancer-type-specific. In BC, elevated miR-205 expression was significantly associated with improved OS [hazard ratio (HR)=0.84, 95% confidence interval (CI): 0.72-0.98, P=0.022]. By contrast, in endometrial cancer, upregulated miR-205 predicted poorer disease-specific survival (HR=2.19, 95% CI: 1.45-3.32, P<0.001), highlighting its dual prognostic role and potential as a therapeutic target

in both malignancies (123). Beyond gynecological cancer, miR-205 also exhibits tumor-suppressive properties in other malignancies. Lu *et al* (124) reported marked downregulation of miR-205 in hepatocellular carcinoma (HCC), especially in aggressive tumor subtypes. Lower miR-205 expression was associated with unfavorable clinicopathological characteristics, and shorter DFS and OS, supporting its role as a tumor suppressor and promising prognostic biomarker in HCC (124).

Therapeutic implications and overcoming chemoresistance

Therapeutic potential in cancer. Beyond its prognostic importance, miR-205 has emerged as a critical modulator of tumor chemoresistance, demonstrating the ability to reverse drug resistance across multiple cancer types (125). The mechanisms underlying this effect frequently involve the inhibition of key resistance-related pathways. For example, in doxorubicin-resistant liver cancer cells (HepG2/DOX), miR-205 overexpression has been shown to restore sensitivity by upregulating PTEN, which suppresses the PI3K/AKT/P-glycoprotein (P-gp) axis and reduces P-gp expression, ultimately inhibiting proliferation and inducing apoptosis (126). Similarly, in BC, miR-205 overcomes tamoxifen resistance by targeting mediator complex subunit 1 (MED1) and HER3, disrupting the HER3-PI3K/AKT-MED1 signaling cascade (127). This chemosensitizing role extends to other agents as well; for example, miR-205 enhances cisplatin sensitivity in glioma by targeting E2F1 (128), and in gallbladder cancer stem cells, its upregulation suppresses both the mRNA and protein levels of PRKCE, thereby inhibiting gemcitabine resistance (129).

Despite their therapeutic potential, the clinical translation of miRNA-based therapies such as miR-205 faces notable challenges, particularly in achieving tumor-specific targeting and efficient *in vivo* delivery. Conventional targeted therapies often encounter issues including drug resistance, adverse side effects and limited efficacy against metastatic disease, underscoring the urgent need for innovative delivery strategies (130). Advances in nanomedicine and natural delivery systems offer promising solutions. Nanoparticle platforms, including zinc oxide and selenium nanoparticles, exhibit intrinsic antitumor properties while serving as carriers for therapeutic agents (131). Additionally, certain plant-derived compounds, such as artemisinin and curcumin, can modulate miRNA expression. Razzaq *et al* (132) demonstrated that miR-205, which is typically downregulated in BC, can be effectively restored using plant extracts, nanoparticles or hybrid plant-nano materials, highlighting the potential of these hybrid strategies to sensitize cancer cells and inhibit tumor progression. Lin *et al* (133) developed a miRNA delivery system utilizing PLGA nanoparticles conjugated with dual cell-penetrating peptides (CPPs, R9 and p28) to target cutaneous squamous cell carcinoma (cSCC). This previous study demonstrated that CPP-conjugated nanoparticles loaded with miR-205 effectively induced tumor regression in a mouse cSCC model and inhibited the migratory ability of cSCC cells. Flow cytometric analysis further revealed that miR-205 upregulation promoted apoptosis in cSCC cells, thereby suppressing tumor growth. These results suggested that such nanoparticle-based miRNA delivery systems represent a promising therapeutic strategy for tumor treatment (133).

Therapeutic potential in non-tumor diseases. Exosomes have emerged as natural delivery vehicles with superior biocompatibility and targeting abilities compared with traditional biomarkers. For instance, Zhang *et al* (134) successfully encapsulated miR-205 within mesenchymal stem cell-derived exosomes, markedly enhancing endothelial barrier function and reducing vascular leakage in an alloxan-induced diabetic mouse model of retinopathy, illustrating a novel, efficient therapeutic approach for vascular diseases. Ybarra *et al* (135) first administered miR-205 mimics to diabetic mice via vitreous cavity injection, observing a notable reduction in VEGF levels. This decrease may be associated with improved erythropoietic processes in abnormal blood vessels. Based on these findings, it was proposed that intravitreal injection of miR-205 may be used as a potential therapy for treating angiogenesis (135). Rubini *et al* (136) employed an exosome-based delivery system to administer miRNAs, including miR-205, as a therapeutic intervention for feline idiopathic cystitis. Following treatment, a substantial proportion of cats exhibited symptom relief within a relatively short period, with ~70% showing clinical improvement by day 15. Ultrasonographic evaluations conducted before and after treatment revealed marked morphological changes in the bladder, characterized by the resolution of intraluminal material and restoration of mucosal integrity. These findings indicated a successful therapeutic outcome following the intervention (136).

Baicalin has been shown to upregulate miR-205 expression in hepatocytes, which subsequently targets and inhibits importin α5, leading to inactivation of the NF-κB signaling pathway. This cascade reduces the release of pro-inflammatory cytokines, alleviates oxidative stress and suppresses hepatocyte apoptosis, thereby attenuating the progression of alcohol-associated liver disease. These findings have demonstrated that certain herbal components can exert hepatoprotective effects by upregulating miR-205, highlighting the therapeutic potential of miR-205 in clinical applications (81). Huang *et al* (50) demonstrated that methylation levels in the miR-205 promoter region were increased in methionine-fed mice and Hcy-treated pulmonary microvascular endothelial cells (PMVECs), leading to reduced miR-205 expression. RT-qPCR results indicated that miR-205 reduction aggravate pulmonary vascular dysfunction. These findings indicated that hypermethylation of the miR-205 promoter may represent a key pathogenic mechanism in Hcy-induced PMVEC dysfunction. Overexpression of miR-205 could serve as a potential therapeutic target for protecting against Hcy-induced pulmonary microvascular dysfunction (50). Zhou *et al* (137) used miRNA microarray and RT-qPCR experiments to determine that miR-205 expression levels were downregulated in fresh endometriotic tissue. Subsequently, miR-205 was upregulated in endometrial cells, and was shown to target and suppress angiopoietin-2 (Ang2) expression, thereby activating the ERK/AKT pathway in ectopic endometrial cells. Ang2 is a growth factor belonging to the Ang/tyrosine kinase with Ig and EGF homology domains signaling pathway, one of the main pathways involved in angiogenesis. This inhibition reduced the migration and invasion of ectopic endometrial stromal cells while promoting apoptosis. These findings demonstrated that miR-205 serves as a novel diagnostic biomarker and therapeutic target for endometriosis treatment (137).

Huang *et al* (49) demonstrated that upregulation of miR-205 expression reduced lipid accumulation and plaque formation in mouse blood vessels, promoted apoptosis and inhibited cell migration in an *in vitro* atherosclerotic cell model constructed from human aortic vascular smooth muscle cells induced by oxidized low-density lipoprotein. These experimental results indicated that miR-205 may be used to mitigate the progression of atherosclerosis (49). Wang *et al* (79) discovered that miR-205 expression was elevated in serum exosomes enriched from patients with occupational dermatitis caused by TCE, and it exhibited a notable positive association with liver function injury markers. Furthermore, in mouse models, miR-205 was shown to target and promote RORα protein expression, thereby exacerbating TCE-induced liver injury. Consequently, therapeutic downregulation of miR-205 expression could potentially mitigate liver damage in these mouse (79). Zhang *et al* (67) established a nasal mucosa of OVA-sensitized mouse model of AR and demonstrated via RT-qPCR that miR-205 expression was upregulated in mice with AR. Notably, miR-205 knockdown reduced nasal rubbing and sneezing frequency while alleviating pathological changes in the nasal mucosa, indicating that miR-205 may serve as a potential therapeutic target for AR (67).

7. Conclusion

miR-205 is a multifunctional regulator involved in a wide range of malignant and non-malignant diseases. It modulates critical signaling pathways that control fundamental cellular processes such as apoptosis, proliferation, migration, angiogenesis and inflammation. The biological effects of miR-205 are highly context-dependent, influenced by its target genes and the specific cellular environment.

In non-malignant conditions, miR-205 serves essential roles in tissue repair, immune-inflammatory regulation, and maintaining epithelial and metabolic homeostasis. Its functions can be paradoxical, for example, it alleviates fibrosis in diabetic nephropathy but may exacerbate inflammation in psoriasis. In cancer, miR-205 dysregulation is closely linked to disease progression, highlighting its potential as a diagnostic and prognostic biomarker, especially via liquid biopsy, as well as a therapeutic target. Targeted delivery of miR-205 mimics or inhibitors using advanced nanocarriers, including exosomes and liposomes, offers promising therapeutic strategies. Additionally, combining miR-205 modulation with conventional treatments may improve therapeutic outcomes.

Overall, research on miR-205 enriches the understanding of disease mechanisms and identifies novel therapeutic options. Translating these findings into clinical practice will require sustained efforts to bridge rigorous basic research with thorough clinical validation.

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Availability of data and materials

Not applicable.

Authors' contributions

DC was responsible for writing the first draft and generating the figures. HD and YS are responsible for reviewing and editing the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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