

MicroRNA regulation of macrophage polarization in lung cancer: Regulatory networks and therapeutic potential (Review)

ZHAO YIMING^{1,2} and LI JIE^{1,2}

¹Clinical Medical College of Beijing University of Chinese Medicine, Beijing 100029, P.R. China; ²Department of Oncology, Guang'anmen Hospital of China Academy of Chinese Medical Sciences, Beijing 100032, P.R. China

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Abstract. Lung cancer is among the most prevalent and fatal cancers worldwide, with its progression heavily shaped by the tumor microenvironment (TME). As key immune cell populations within the TME of lung cancer, macrophages are involved in the entire process of tumor initiation and development. Macrophage polarization serves as a critical link between inflammation and tumorigenesis and is broadly divided into classically activated M1 and alternatively activated M2 phenotypes. These phenotypes exert tumor-suppressive and tumor-promoting effects, respectively, by secreting distinct cytokine profiles. MicroRNAs (miRNAs/miRs) are a class of endogenous small non-coding RNAs that play broad roles in the malignant progression of lung cancer by regulating various cellular processes, including proliferation, resistance to apoptosis, and metabolic reprogramming. Emerging evidence suggests that miRNAs such as miR-335-5p, miR-106a-5p and miR-99b regulate M1/M2 macrophage polarization by targeting key pathways in lung cancer. Through these regulatory events, miRNAs exert synergistic effects on multiple tumor hallmarks, including proliferation, invasion, migration, apoptosis, angiogenesis, cell cycle progression, stemness maintenance, and epithelial-mesenchymal transition. Collectively, these events drive lung cancer progression and influence therapeutic efficacy. The present review synthesizes recent discoveries to explore the relationship between macrophage polarization and lung cancer, with a specific focus on miRNA-mediated regulatory mechanisms in lung cancer therapy. Ultimately, the present review aimed to provide new insight and a reference point to inform future prevention and treatment strategies for lung cancer.

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1. Introduction

Lung cancer, the most lethal malignancy worldwide, continues to place an increasing burden on healthcare systems. Globally, 2022 witnessed >2.8 million new cases and 1.8 million deaths, accounting for almost 18% of all cancer-related fatalities (1). Despite therapeutic advances, several barriers continue to hinder the long-term survival of patients with lung cancer, including resistance to targeted therapies, off-target effects, low response rates to immune checkpoint inhibitors and chemotherapy-related toxicity (2). Hence, an in-depth exploration of intercellular communication mechanisms within the tumor microenvironment (TME) and the identification of novel intervention targets are of utmost importance for overcoming therapeutic bottlenecks in lung cancer. Macrophages represent the most abundant immune cell population infiltrating the lung cancer microenvironment. Characterized by high plasticity, they can polarize into anti-tumor M1 or pro-tumor M2 phenotypes (3). Macrophage polarization exhibits dynamic evolution during lung cancer progression: It is initially dominated by the M1 phenotype, exerting antitumor effects; however, as the tumor advances, it gradually shifts toward the M2 phenotype, driving immune escape through mechanisms such as promoting tumor cell metastasis, angiogenesis, and inhibiting T-cell function, ultimately contributing to a tumor-promoting microenvironment (4). Therefore, targeting the polarization of M1/M2 macrophages is a key therapeutic target for lung cancer. Certain drugs, such as artemether and CLMSR nanoparticles can induce M1/M2 reprogramming, restore and enhance their phagocytic function and antigen-presenting ability, thereby activating antitumor

Correspondence to: Professor Li Jie, Department of Oncology, Guang'anmen Hospital of China Academy of Chinese Medical Sciences, 5 Beixiang, Xicheng, Beijing 100032, P.R. China
E-mail: drjieli2007@126.com

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immune responses and exerting potent anti-lung cancer activity (5,6). MicroRNAs (miRNAs/miRs) are a class of non-coding RNAs ~22 nucleotides in length, which regulate the expression of target genes at the post-transcriptional level and are widely involved in biological processes including cell differentiation, proliferation, and immune response (7). A previous study demonstrated that miRNAs serve as key molecular switches that regulate macrophage polarization (8). Moreover, several tumor-suppressing miRNAs, such as miR-7, miR-34a and the let-7 family, have been proven to inhibit the proliferation and migration of lung cancer cells and induce their apoptosis, thereby exerting anti-cancer effects (9,10). Thus, modulating miRNA expression to restore the M1/M2 balance may produce beneficial anti-lung cancer outcomes.

2. Overview of miRNAs

Biosynthesis of miRNAs. miRNAs are a class of small non-coding RNAs widely present in eukaryotes. They negatively regulate gene expression at the post-transcriptional level by binding to target mRNAs, thereby promoting mRNA degradation or inhibiting translation (11). The biosynthesis of miRNAs is an orderly multi-step process. Firstly, in the cell nucleus, miRNA genes are transcribed by RNA polymerase II to generate primary miRNA (pri-miRNA) with a stem-loop structure; subsequently, these pri-miRNAs are cleaved by the Drosha ribonuclease III-DiGeorge syndrome critical region 8 complex to form precursor miRNAs (pre-miRNAs) with a length of ~70 nucleotides. Secondly, these pre-miRNAs are transported from the cell nucleus to the cytoplasm through a mechanism dependent on Exportin-5. Finally, in the cytoplasm, these pre-miRNAs are further cleaved by the Dicer enzyme, ultimately forming mature miRNA double strands with ~22 nucleotides. One of these strands is selectively loaded onto the RNA-induced silencing complex (RISC). Functionally, the RISC carrying the mature miRNA mainly mediates partial complementarity with the target mRNA, promoting the demethylation-dependent degradation of the target mRNA and inhibiting its translation, thereby achieving post-transcriptional negative regulation of gene expression. Through this mechanism, miRNAs are widely involved in processes, such as cell proliferation, differentiation, apoptosis and the maintenance of cell homeostasis (12,13).

Regulatory role of miRNAs in the occurrence and development of lung cancer. As a key regulator of gene expression, miRNAs are involved in diverse biological processes, including cell proliferation, differentiation, apoptosis and immune regulation. The aberrant expression of miRNAs is closely associated with various diseases (14). In the context of malignant tumors, miRNA plays a critical role in tumor initiation, progression, proliferation and metastasis, exhibiting both tumor-suppressive and oncogenic functions, and thus hold potential as tools for diagnosis, treatment and prognostic assessment (15). Furthermore, miRNAs can interact with extracellular vesicles, high-density lipoproteins and RISC effector proteins, allowing them to remain stable in extracellular fluids and positioning them as promising disease biomarkers with broad application potential (16). A growing body of evidence has identified multiple miRNAs as key biomarkers for lung cancer (17),

where they exert key regulatory functions in processes, such as apoptosis, drug resistance, proliferation, invasion and migration, thereby actively participating in lung cancer pathogenesis and progression (18-20).

3. Overview of macrophage polarization

Macrophages, first discovered in 1908 for their phagocytic activity, are essential components of the innate immune response (21). Beyond their well-established roles in phagocytosis, exogenous antigen presentation and cytokine secretion, macrophages also participate in systemic metabolism, hematopoiesis, angiogenesis and malignant tumor progression (22). Under distinct microenvironmental stimuli, macrophages polarize into classical activated M1 or alternative activated M2 phenotypes. M1 macrophages, induced by granulocyte-macrophage colony-stimulating factor (GM-CSF), Toll-like receptor (TLR) ligands, or T-helper 1 cell (Th1) cytokines, exhibit a high expression of pro-inflammatory cytokines (e.g., TNF- α , IL-1 β , IL-6, IL-12 and IL-23) and surface molecules (CD40, CD64, CD68, CD80, CD86 and HLA-DR). They exhibit potent antigen-presenting capacity, driving inflammation, pathogen clearance and antitumor immunity (23). M2 macrophages are primarily induced by Th2-type cytokines (IL-4/IL-13), immune complexes, glucocorticoids, or adenosine, and play central roles in anti-inflammatory responses, immune regulation and tissue repair and remodeling. According to the nature of inducing stimuli and resultant functional profiles, M2 macrophages are categorized into four subtypes: M2a, M2b, M2c and M2d. Specifically, M2a macrophages, induced by IL-4 or IL-13, highly expresses CD206 and CD209 and is primarily involved in Th2-type immune responses, allergic reactions and anti-parasitic immunity. M2b macrophages, induced by immune complexes combined with TLR ligands, exhibit both pro-inflammatory and anti-inflammatory characteristics, with a high expression of IL-10 and TNF- α , playing a unique role in immune regulation. M2c macrophages, induced by IL-10, transforming growth factor- β (TGF- β), or glucocorticoids, represent the primary subtype associated with acquired immune regulation, highly expressing CD163 and CD206, and various scavenger receptors, and are crucial for the phagocytosis of apoptotic cells and tissue remodeling. M2d macrophages, induced by TLR ligands in combination with adenosine analogs, are primarily associated with angiogenesis and tumor progression, with a high expression of vascular endothelial growth factor (VEGF) and IL-10 (24). At the molecular level, M2 macrophages secrete a range of anti-inflammatory cytokines and chemokines, including TGF- β , IL-10, C-C motif chemokine ligand (CCL)18 and CCL22. They also highly express characteristic surface markers, such as CD163, CD206, CD209, scavenger receptor A, scavenger receptor class B type I and CCL2. Through these molecules, M2 macrophages not only efficiently clear apoptotic cells and debris, but also participate in tissue repair and matrix remodeling by secreting pro-fibrotic factors, such as TGF- β and fibronectin (25,26). Studies have shown that in early-stage lung cancer, M1 macrophages predominate and inhibit lung cancer cell growth through the expression of various pro-inflammatory cytokines, chemokines and effector molecules. By contrast, advanced-stage lung cancer is

characterized by a progressive shift toward the M2 phenotype, in which M2 macrophages promote tumor growth, invasion and metastasis (27). Therefore, targeting the inhibition of the M2 phenotype and inducing M2-to-M1 repolarization to correct the imbalance of macrophage polarization represents a promising strategy for the prevention and treatment of lung cancer. However, it should be noted that this strategy still faces several challenges in practical application (28). Firstly, the TME is characterized by hypoxia, the accumulation of lactic acid and various immunosuppressive factors, such as IL-4, IL-10 and TGF- β (29). These factors may continuously hinder the reversal of M2 to M1 polarization state, thereby severely reducing the efficiency of re-polarization. Secondly, the re-polarized M1 phenotype may lack long-term stability. The TME continuously activates signaling pathways, such as STAT6 and PI3K-AKT-mTOR, which prompt macrophages to transform into the M2 phenotype (30). This not only reduces the initial re-polarization effect, but also diminishes the ability of the polarized M1 cells to maintain a stable antitumor state under the influence of dynamic microenvironmental signals (31). Furthermore, the excessive activation of M1-type macrophages can induce tissue inflammatory damage and, in certain advanced tumor contexts, may even paradoxically promote malignant progression (32). Therefore, future investigations are warranted to elucidate the molecular regulatory networks governing polarization reversal, systematically assess its maintainability and safety within the complex *in vivo* microenvironment, and explore optimization strategies in combination with other therapeutic modalities. This may provide a more robust theoretical foundation for the clinical translation of this approach. The mechanisms of macrophage polarization are illustrated in Fig. 1.

4. Regulatory effects of macrophage polarization on lung cancer

Macrophage polarization profoundly affects the occurrence, development and therapeutic efficacy of lung cancer by regulating multiple biological processes, such as proliferation and invasion of lung cancer cells, apoptosis, angiogenesis, cell cycle progression, the maintenance of tumor stemness and epithelial-mesenchymal transition (EMT). The mechanisms by which macrophage polarization regulates lung cancer are illustrated in Fig. 2.

Regulation of the proliferation, invasion and migration of lung cancer cells. The proliferation, invasion and migration of lung cancer cells represent core processes driving malignant tumor progression (33). In non-small cell lung cancer (NSCLC), exosomes derived from M2 macrophages have been shown to enhance tumor cell viability, migration and invasion by carrying miRNAs, such as miR-155 and miR-196a-5p (34). C-X-C motif chemokine ligand 9 (CXCL9) inhibits the proliferation, migration, metastasis and invasion of lung cancer cells by suppressing the polarization and function of M2 macrophages (35). Furthermore, octamer-binding transcription factor 4 (OCT4)-expressing lung cancer cells can induce macrophage polarization toward the M2 phenotype by upregulating CSF levels, thereby facilitating tumor growth, infiltration and metastasis (36).

Regulation of the apoptosis of lung cancer cells. Apoptosis is a genetically regulated program of cell death that plays a critical role in maintaining tissue homeostasis, eliminating abnormal cells and modulating tumor development. The induction of apoptosis in tumor cells represents a key mechanism underlying chemotherapy, targeted therapy and immunotherapy for lung cancer (37). The polarization state of macrophages serves as a critical microenvironmental factor that regulates apoptosis in lung cancer cells, with M1 and M2 macrophages exerting opposing pro-apoptotic and anti-apoptotic effects, respectively, through distinct molecular mechanisms. M1 macrophages secrete interferon- γ (IFN- γ), which activates the Janus Kinase 1 (JAK1)/signal transducer and activator of transcription 1 (STAT1) signaling pathway. This activation promotes interaction between STAT1 and tumor protein p53, reduces p53 binding to mouse double minute 2 homolog, inhibits p53 ubiquitination and degradation, and enhances p53 stability and transcriptional activity, leading to the upregulation of pro-apoptotic molecules, such as PUMA and initiation of the mitochondrial apoptotic pathway (38). Furthermore, IFN- γ also induces an increase in reactive oxygen species levels within lung cancer cells, causing DNA damage and activating the ataxia telangiectasia mutated/checkpoint kinase 2 pathway. These two pathways converge at the p53/PUMA axis, synergistically amplifying apoptotic signaling and collectively inducing lung cancer cell death (39). By contrast, M2 macrophages secrete anti-inflammatory cytokines, including IL-10 and TGF- β , which suppress antitumor immune responses and attenuate immune cell-mediated tumor cell killing, thereby inhibiting tumor cell apoptosis and promoting tumor cell survival (40).

Regulation of angiogenesis in lung cancer. Angiogenesis plays a critical role in the progression and metastasis of lung cancer. Intervening in tumor angiogenesis and promoting vascular normalization have emerged as effective strategies to inhibit LUAD growth (41). In lung cancer tissues, tumor-associated macrophages (TAMs) typically polarize toward the M2 phenotype, thereby promoting abnormal blood vessel formation and accelerating tumor invasion and dissemination (42). Macrophage polarization exerts opposing effects on tumor angiogenesis: M2 macrophages generally promote aberrant vascularization through the secretion of pro-angiogenic factors, thereby driving tumor progression, whereas M1 macrophages typically suppress angiogenesis and exert anti-tumor effects (43,44). Exosomes secreted by M2 macrophages can be taken up by LUAD cells, and the miRNAs encapsulated within these exosomes further promote the invasion, migration and aberrant vascularization of LUAD cells (45). In LUAD, membrane-spanning 4-domains subfamily A member 1 has been shown to regulate M1 polarization, macrophage migration and angiogenesis, thereby exerting an inhibitory effect on blood vessel formation (46).

Regulation of cell cycle progression in lung cancer cells. The cell cycle is a core biological process governing cell growth, division and proliferation. Dysregulation of the cell cycle represents a key driving force in the initiation and progression of lung cancer, and arresting cell cycle progression in lung cancer cells can delay malignant tumor progression (47). Macrophage

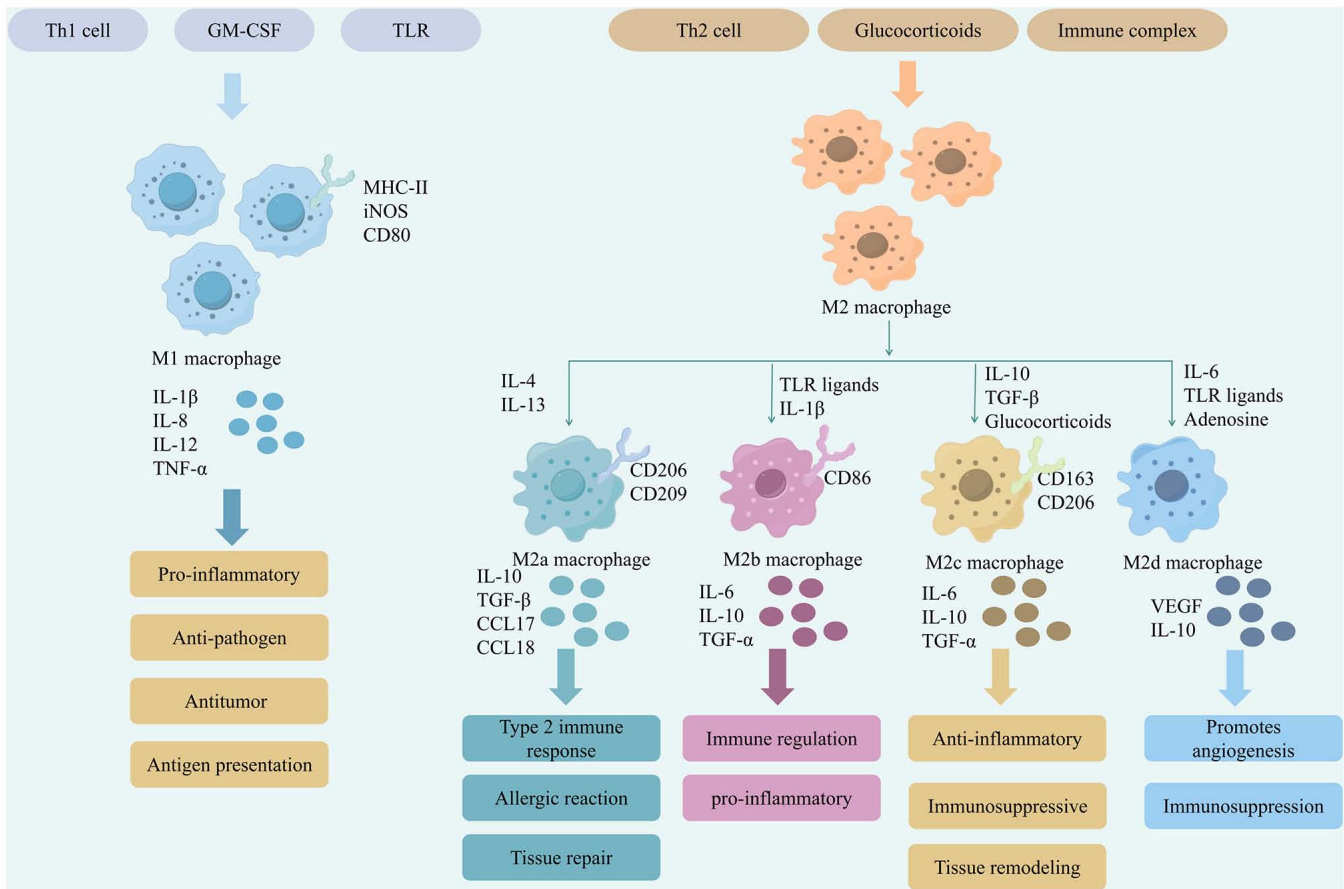


Figure 1. Mechanisms of macrophage polarization. The image presents the complete regulatory network for macrophage polarization. Under the guidance of Th1 and Th2 cells and GM-CSF and other signals, macrophages can polarize into the pro-inflammatory M1 type (induced by TLR ligands, expressing CD80/CD86/iNOS, secreting IL-1 β , TNF- α , etc., with anti-pathogen and anti-tumor functions), as well as four M2 subtypes: M2a (induced by IL-4/IL-13, involved in type 2 immunity and allergy), M2b (induced by immune complexes, having both immunoregulatory and pro-inflammatory effects), M2c (induced by glucocorticoids/IL-10, mediating immunosuppression and tissue repair), and M2d (induced by TLR ligands/adenosine, promoting angiogenesis). The figure systematically reveals the functional diversity of macrophages in inflammation, immune regulation and tissue remodeling. GM-CSF, granulocyte-macrophage colony-stimulating factor; TLR, Toll-like receptor; iNOS, inducible nitric oxide synthase; MHC-II, major histocompatibility complex class II.

polarization profoundly influences the proliferative fate of lung cancer cells by modulating the expression of cell cycle checkpoints and cycle-related proteins. Accumulating evidence indicates that M1 and M2 macrophages exert opposing effects on the cell cycle of lung cancer cells. Promoting M1 macrophage polarization can induce cell cycle arrest (e.g., S-phase arrest), thereby exerting antitumor effects (48,49). By contrast, inducing M2 polarization promotes G1/S transition and accelerates cell cycle progression, driving lung cancer proliferation (50,51).

Regulation of stemness maintenance in lung cancer cells. Emerging evidence indicates that cell stemness is not only involved in the initiation and progression of lung cancer, but also represents a major contributor to treatment failure (52). The polarization state of macrophages plays a critical regulatory role in maintaining the stemness of lung cancer cells. M2 macrophages induce the expression of stemness markers in lung cancer cells by secreting cytokines and activating associated signaling pathways, thereby enhancing their self-renewal capacity and tumorigenicity. By contrast, M1 polarization helps suppress the acquisition of stemness characteristics (53). Tumor necrosis factor- α -induced protein-8-like factor 2 (TIPE2) has

been shown to exert antitumor effects by inhibiting M2 macrophage polarization, thereby suppressing stemness in lung cancer cells (54). Furthermore, M2 macrophages can significantly upregulate the expression of stemness-related genes in lung cancer cells, further promoting disease progression (55).

Regulation of EMT in lung cancer cells. EMT is a critical process through which lung cancer cells acquire migratory and invasive capabilities, driving the aggressive behavior of NSCLC and representing a core mechanism underlying poor prognosis and high mortality (56). Macrophage polarization, through its distinct subtypes, plays a crucial regulatory role in EMT of lung cancer cells. M2 macrophages have been shown to directly induce EMT in A549 cells, characterized by the upregulation of vimentin and fibronectin, and the downregulation of E-cadherin, a process closely associated with the activation of the NF- κ B pathway (57). Additionally, IL-6 secreted by M2 macrophages enhances the expression of cyclooxygenase-2 and prostaglandin E2 (PGE2) in lung cancer cells, with PGE2 subsequently promoting β -catenin nuclear translocation and inducing EMT (58). Within the lung cancer microenvironment, M2 macrophages initiate the EMT program through the secretion of a panel of cytokines, among

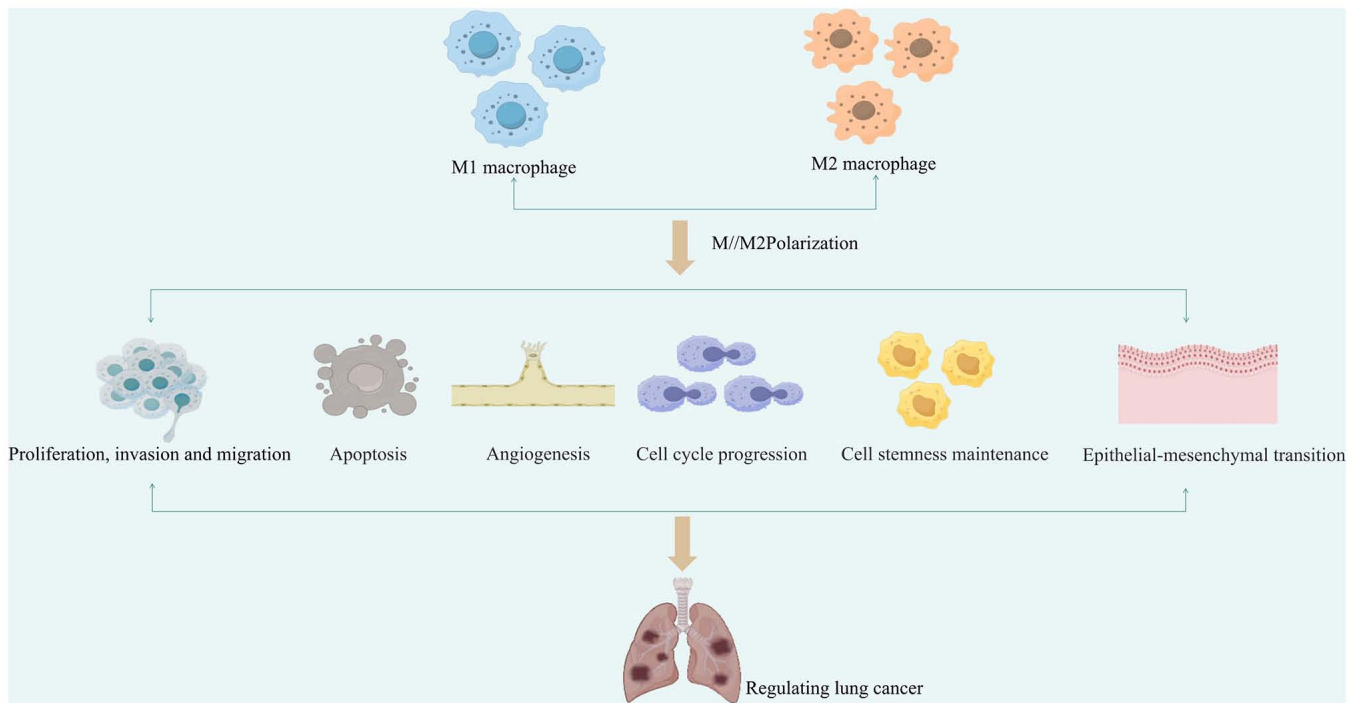


Figure 2. Mechanisms underlying the regulation of lung cancer by macrophage polarization. The image illustrates that macrophage polarization profoundly affects the occurrence and development of lung cancer by regulating multiple key biological processes, such as the proliferation, invasion and migration, apoptosis, angiogenesis, cell cycle progression, stem cell maintenance and the epithelial-mesenchymal transition of lung cancer cells.

which TGF- β , IL-6 and CCL2 have been identified as key mediators. These factors act directly on lung cancer cells to activate EMT-associated transcriptional programs (59). The polarized M2 macrophages secrete cytokines such as IL-10 and TGF- β , which further promote the EMT of NSCLC cells (60). Moreover, M1 macrophages can inhibit the EMT process by modulating the IFN- γ /JAK1/STAT1 pathway and reducing the expression of EMT-related transcription factors (61).

5. miRNA-mediated regulation of macrophage polarization in lung cancer

Therapeutic roles of miRNAs in regulating macrophage polarization in lung cancer. Researchers have found that miR-99b and miR-let-7b-5p, as well as the upregulation of miR-135a-5p, miR-770 and miR-613 can exert an attenuating effect on the growth and metastasis of lung cancer. The mechanisms by which miRNAs regulate macrophage polarization for lung cancer therapy are illustrated in Fig. 3.

miR-99b has been shown to participate in the progression of various tumors owing to its potent immunomodulatory functions (62). In the microenvironment of lung cancer, miR-99b regulates the polarization state of macrophages, thereby influencing the efficiency of anti-tumor immune response. NF- κ B and mTOR are key downstream molecules through which miR-99b regulates macrophage polarization, with mTOR identified as a direct target gene of miR-99b (63). The upregulation of miR-99b suppresses κ B-Ras2, subsequently activating NF- κ B signaling and boosting TNF- α , IL-6 and IL-12, and major histocompatibility complex class II expression, all of which promote M1 polarization. Concurrently, the elevated expression of miR-99b inhibits mTOR and its downstream

interferon regulatory factor (IRF)4, blocking the mTOR/IRF4 axis and reducing arginase-1 (Arg-1) and Mannose receptor (MR) expression, thereby restraining M2 polarization (64). Moreover, these changes improve macrophage phagocytosis and antigen presentation, significantly delaying tumor growth in a mouse transplanted tumor model (64). The let-7 family of miRNAs is recognized as a class of tumor suppressors that play critical regulatory roles in the initiation and progression of various cancers (65). Specifically, let-7b-5p has been shown to inhibit M2 polarization and enhance the phagocytic activity of macrophages, thereby suppressing tumor growth (66). The adaptor-related protein complex 1 subunit sigma 1 (AP1S1) functions as a key regulator of intracellular vesicle transport, and its aberrant expression is closely associated with tumor progression, immune evasion and malignant behavior (67). In lung cancer, the dysregulation of AP1S1 may interfere with the antitumor immune response by affecting vesicle transport. A previous study co-cultured A549-derived extracellular vesicles (EVs) with phorbol 12-myristate 13-acetate (PMA)-induced differentiated THP-1 macrophages for 48 h *in vitro*. They observed that the EV-delivered hsa-let-7b-5p could directly target and inhibit the expression of AP1S1, thereby regulating the AP1S1/p53 signaling pathway (68). Specifically, the EVs can target and inhibit AP1S1 expression, leading to upregulation of CD86 and inducible nitric oxide synthase (iNOS), the downregulation of CD206, Arg-1, TGF- β and IL-10, and the subsequent inhibition of M2 polarization. Additionally, this regulation increases E-cadherin expression, decreases N-cadherin and vimentin levels and suppresses EMT, while also inhibiting the proliferation, invasion and migration of A549 and H1299 cells (68). The activation of the STAT signaling pathway mediates IL-4 secretion regulated

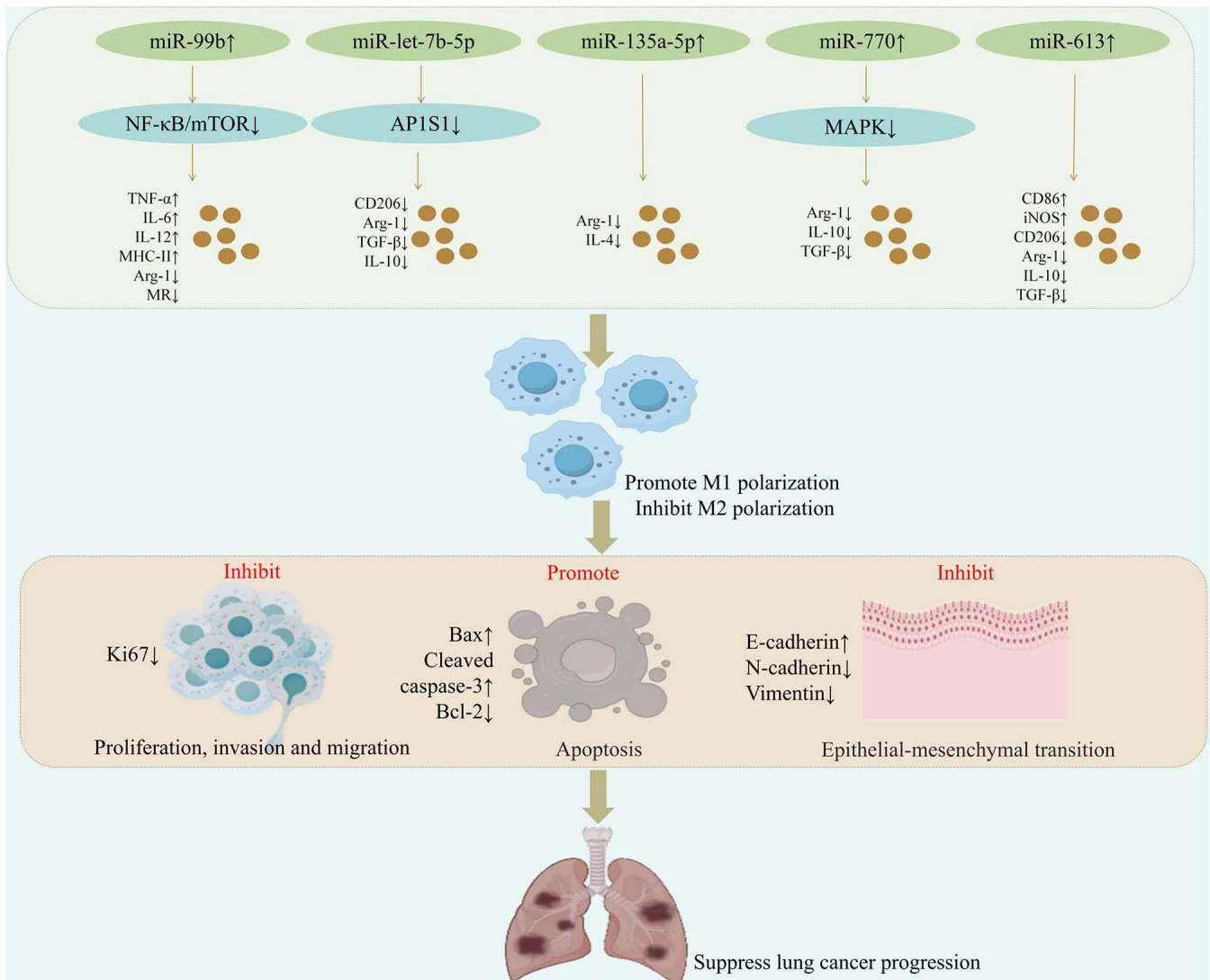


Figure 3. Mechanisms of miRNA-mediated regulation of macrophage polarization in lung cancer therapy. The image illustrates that miR-99b, miR-let-7b-5p, as well as the upregulation of miR-135a-5p, miR-770 and miR-613 expression can induce M1 polarization and inhibit M2 polarization, thereby synergistically inhibiting the proliferation, invasion and migration of lung cancer cells, inhibiting epithelial-mesenchymal transition, and promoting cell apoptosis, thus significantly delaying the growth and metastasis of lung cancer. MHC-II, major histocompatibility complex class II; Arg-1, arginase-1; MR, mannose receptor.

by GATA binding protein 3 (GATA3), a process that plays a crucial role in inducing M2 macrophage polarization (69). In the microenvironment of lung cancer, M2-type TAMs maintain an immunosuppressive state by secreting cytokines such as IL-4, thereby facilitating tumor immune escape. miR-135a-5p has been demonstrated to exert tumor-suppressive effects in various malignancies (70,71). The upregulation of miR-135a-5p expression reduces the levels of STAT6, p-STAT6, GATA3 and IL-4, thereby inhibiting the STAT6/GATA3/IL-4 signaling pathway, which in turn decreases Arg-1 expression and suppresses M2 macrophage polarization, thereby alleviating the immunosuppression mediated by M2-type TAMs in lung cancer. Additionally, this upregulation increases E-cadherin expression and decreases vimentin expression, thereby attenuating the proliferative, invasive and migratory abilities of tumor cells (72). Furthermore, *in vivo* experiments using xenograft models have confirmed that the upregulation of miR-135a-5p expression downregulates Arg-1 levels in tumor tissues, inhibits M2 macrophage polarization, and significantly

impedes tumor growth and metastasis (72). This confirms that miR-135a-5p exerts a dual antitumor effect in lung cancer by simultaneously reversing the immunosuppressive microenvironment and inhibiting the malignant behavior of tumor cells (72). miR-770 has been shown to inhibit tumorigenesis and EMT in NSCLC (73). The MAPK signaling pathway is known to be involved in tumor cell growth, migration and invasion. In NSCLC, the abnormal activation of the MAPK pathway is closely associated with the malignant progression of the tumor and poor prognosis (74). The upregulation of miR-770 expression targets and downregulates MAP3K1, thereby inhibiting the MAPK signaling pathway. This leads to reduced expression of Arg-1, IL-10 and TGF-β, resulting in suppression of M2 macrophage polarization, and this regulation helps to reverse the immunosuppressive microenvironment. Additionally, miR-770 upregulation increases E-cadherin expression while decreasing vimentin and N-cadherin expression, thereby inhibiting EMT, and this is of utmost significance in preventing the epithelial-derived tumor cells of NSCLC

from acquiring mesenchymal phenotypes and migratory abilities. Moreover, it induces apoptosis in K-MES-1, A549 and NCI-H1650 cells, significantly reducing their viability and suppressing proliferation, invasion and migration (75). In xenograft mouse models, the upregulation of miR-770 expression has been shown to downregulate CD206 expression and inhibit M2 macrophage polarization, while also inducing apoptosis in tumor tissues and reducing Ki-67 expression, thereby suppressing tumor growth (75). This indicates that this miRNA exerts an antitumor effect in NSCLC by simultaneously promoting immune remodeling and directly inhibiting the malignant phenotype of the tumor (75). miR-613 exerts antitumor effects in various malignancies (76). The upregulation of miR-613 expression reduces the levels of CD206, Arg-1, IL-10 and TGF- β , while increasing the expression of CD86 and iNOS, thereby inhibiting M2 macrophage polarization and promoting M1 polarization, and this polarization remodeling helps to shift TAMs from a tumor-promoting phenotype to a tumor-suppressing phenotype (77). Additionally, miR-613 upregulation suppresses the proliferation, invasion and migration of A549, HCC827, H1299 and H1650 cells, while also increasing the expression of Bax and cleaved caspase-3, and decreasing Bcl-2 expression, thereby promoting the apoptosis of these cells (77). This indicates that miR-613 exerts a dual tumor-suppressing effect in lung cancer by reprogramming the polarization balance of macrophages and directly inducing apoptosis of tumor cells (77).

Pathogenic roles of miRNAs in regulating macrophage polarization in lung cancer. During the progression of lung cancer, the dysregulation of miRNA expression plays a crucial role in regulating macrophage polarization. On the one hand, the upregulation of miR-106a-5p, miR-21-5p, miR-3153, miR-146a, etc., can inhibit M1 polarization, promote M2 polarization, and promote the proliferation, invasion and migration of lung cancer cells, induce EMT, inhibit lung cancer cell apoptosis, and promote lung cancer angiogenesis. On the other hand, the downregulation of miR-335-5p, miR-4319, miR-103a, miR-155, miR-132-3p, etc., can inhibit M1 polarization, promote M2 polarization and synergistically enhance the maintenance of lung cancer cell stemness, cell cycle progression and EMT, ultimately accelerating tumor growth and metastasis. The mechanisms by which miRNAs regulate macrophage polarization to promote lung cancer are illustrated in Fig. 4.

Regulation of macrophage polarization by miRNAs driven by the hypoxic microenvironment. Obstructive sleep apnea (OSA) is one of the most common sleep-disordered breathing conditions, characterized by intermittent hypoxia (IH). Previous research has demonstrated that OSA is closely associated with the progression of lung cancer (78). On the one hand, exosomes derived from the blood of patients with OSA can directly promote the proliferation, invasion and migration of lung cancer TC1 cells (78). On the other hand, intermittent hypoxia, as the core pathological feature of OSA, has been demonstrated to indirectly enhance the malignant phenotype of TC1 cells by regulating macrophage polarization (79). miR-106a-5p expression has been reported to be elevated in NSCLC (80). IH can upregulate miR-106a-5p expression, inhibits phosphatase and tensin homolog (PTEN) and activates the STAT3 signaling pathway. This cascade

leads to the upregulation of CD206, CD163, Arg-1, TGF- β 1, IL-6, CXCR4 and CCL2, along with the downregulation of iNOS, collectively promoting macrophage polarization toward the M2 phenotype (81). Consequently, this enhances the proliferation, invasion and migration of A549 and NCI-H226 cells, while simultaneously downregulating E-cadherin expression and upregulating N-cadherin and vimentin expression, thereby inducing EMT and ultimately driving NSCLC progression (81). These findings reveal the molecular mechanism by which OSA-related intermittent hypoxia reprograms macrophage polarization through the miR-106a-5p/PTEN/STAT3 axis and promotes the malignant phenotypic transformation of tumors, providing a theoretical basis for targeted intervention in patients with OSA and NSCLC. Hypoxia is a hallmark feature of the TME. Tumor-derived exosomes under hypoxic conditions can remodel the TME, promoting tumor progression, angiogenesis and pre-metastatic niche formation (82). Suppressor of cytokine signaling 3 (SOCS3) is a key regulator of innate and adaptive immunity and plays a particularly crucial role in macrophage polarization. In lung cancer, the dysregulation of SOCS3 expression may disrupt the immune balance and thereby promote immune escape (83). miR-1290 targets and inhibits SOCS3 expression, leading to the activation of the STAT3 signaling pathway (84). This results in increased expression of CD163, CD206 and IL-10, along with the decreased expression of CD80 and monocyte chemoattractant protein-1 (MCP-1), thereby promoting macrophage polarization toward the M2 phenotype, and this polarization process further exacerbated the immunosuppressive state in the lung cancer microenvironment (84). Additionally, the upregulation of miR-1290 significantly enhances the proliferation, invasion and migration of A549 and H1299 lung cancer cells. In a mouse xenograft model, the overexpression of miR-1290 markedly accelerates tumor growth. These findings further confirm that the hypoxia-induced miR-1290/SOCS3/STAT3 axis promotes tumor formation by reprogramming macrophages to the M2 phenotype and directly facilitating the malignant behavior of lung cancer cells (84). IRF1 is a key transcription factor involved in macrophage polarization and is regulated by multiple miRNAs (85). miR-21 has been shown to regulate lung cancer progression and EMT (86). The abnormal activation of the PI3K/AKT pathway is closely associated with cell survival, proliferation, and the establishment of an immunosuppressive microenvironment in lung cancer (87). Under hypoxic conditions, miR-21 targets and inhibits IRF1 expression, leading to the increased phosphorylation of PI3K and AKT, and the subsequent activation of the PI3K/AKT signaling pathway. This cascade upregulates the expression of CD163, CD206, Arg-1, IL-10 and TGF- β , thereby promoting M2 macrophage polarization; this polarization process further strengthens the immunosuppressive microenvironment, creating favorable conditions for the immune escape and malignant progression of lung cancer; at the same time, it enhances the proliferative, invasive and migratory abilities of H1299 lung cancer cells (87). In a mouse subcutaneous tumor model, the overexpression of miR-21 under hypoxic conditions was shown to significantly enhance the proliferative capacity of H1299 cells and accelerate tumor growth (87). This further confirms that the hypoxia-induced miR-21/IRF1/PI3K/AKT axis, by inhibiting the antitumor immune response mediated

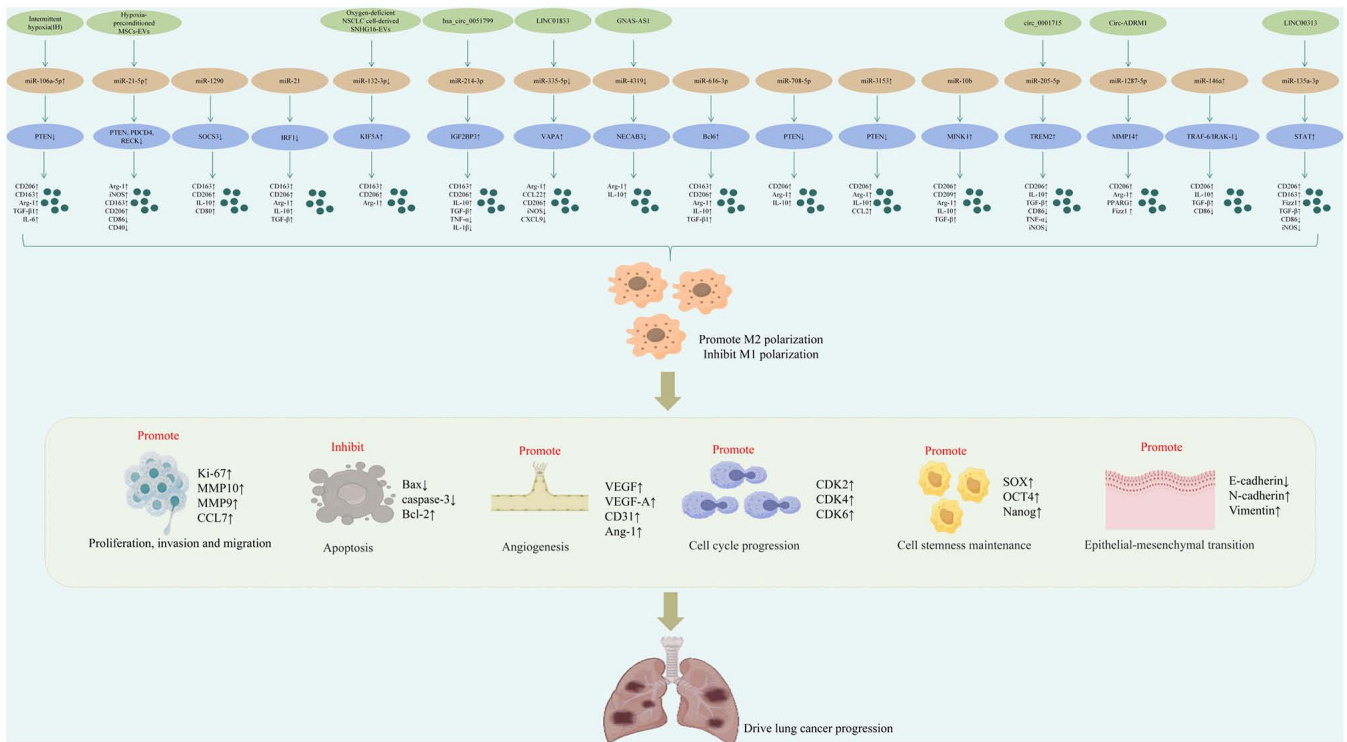


Figure 4. Mechanisms by which miRNAs regulate macrophage polarization to promote lung cancer progression. The image illustrates shows that the upregulation of miR-106a-5p, miR-21-5p, miR-3153 and miR-146a can inhibit M1 polarization, promote M2 polarization, and promote the proliferation, invasion and migration of lung cancer cells, induce EMT, and inhibit lung cancer cell apoptosis, while promoting lung cancer angiogenesis. In addition, downregulation of miR-335-5p, miR-439, miR-103a, miR-155, and miR-132-3p can inhibit M1 polarization, promote M2 polarization, and synergistically enhance the maintenance of lung cancer cell stemness, cell cycle progression and EMT, ultimately accelerating tumor growth and metastasis. EMT, epithelial-mesenchymal transition; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; VAPB, vesicle-associated membrane protein-associated protein B; NECAB3, N-terminal EF-hand type calcium-binding protein 3; PTEN, phosphatase and tensin homolog; MINK1, misshapen-like kinase 1; TREM2, triggering receptor expressed on myeloid cells 2; TRAF6, TNF receptor-associated factor 6; IRAK1, interleukin-1 receptor-associated kinase 1.

by IRF1 and promoting M2 polarization, collaboratively drives the malignant progression of lung cancer. miR-214-3p can directly target oncogenes, thereby inhibiting the malignant progression of LUAD (88). The hypoxic microenvironment promotes the release of exosomal hsa_circ_0051799; this suggests that hypoxia may impair the tumor-suppressive function of miR-214-3p through a circRNA-mediated mechanism. Further mechanistic investigations have revealed that hsa_circ_0051799 directly targets miR-214-3p, leading to the upregulation of insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) and the subsequent activation of the JAK/STAT3 signaling pathway, as evidenced by the increased p-JAK2/JAK and p-STAT3/STAT ratios. This cascade results in the upregulated expression of CD163, CD206, IL-10, and TGF- β , thereby promoting M2 macrophage polarization, while concurrently downregulating TNF- α , IL-1 β , MCP-1 and IL-12, thereby inhibiting M1 macrophage polarization; this polarization imbalance has significantly exacerbated the immunosuppressive state in the microenvironment of LUAD. Additionally, it upregulates vimentin expression and downregulates E-cadherin expression, inducing EMT. Furthermore, it significantly inhibits apoptosis in A549, PC-9, H1975 and H1395 cells, while enhancing their proliferative, invasive and migratory capabilities (89). These findings were further validated in a xenograft model using nude mice (89). The aforementioned results confirm that the hypoxia-induced hsa_circ_0051799/miR-214-3p/IGF2BP3/JAK-STAT3 axis

drives the malignant progression of LUAD through multiple mechanisms, such as reprogramming macrophage polarization balance, inducing EMT and promoting tumor cell survival. Long non-coding RNA GNAS-AS1 has been shown to play a role in tumor progression (90). Bioinformatics predictions have indicated that miR-439 is a potential binding target of GNAS-AS1. N-terminal EF-hand type calcium-binding protein 3 (NECAB3) plays a critical role in tumorigenesis by promoting the activation of hypoxia-inducible factor-1 (HIF-1) (91). In lung cancer, the abnormal activation of the HIF-1 signaling pathway is one of the core steps that enable the tumor to adapt to the hypoxic microenvironment, promote metabolic reprogramming, and drive malignant progression. As a competitive endogenous RNA (ceRNA), GNAS-AS1 can sponge and downregulate the expression of miR-439, thereby relieving the translation inhibitory effect of miR-439 on NECAB3 and subsequently upregulating the expression of NECAB3. This cascade increases the expression of Arg-1 and IL-10, thereby promoting M2 macrophage polarization; this polarization process further intensifies the immunosuppressive state in the lung cancer microenvironment, creating favorable conditions for tumor immune escape and malignant progression, while also enhancing the proliferation, invasion and migration of A549 and H1299 cells (92).

Regulation of macrophage polarization by miRNAs mediated by lung cancer-derived exosomes. Mesenchymal stem cells (MSCs) are a group of highly heterogeneous precursor

cells characterized by their anti-inflammatory, wound-healing-promoting and homeostasis-maintaining properties (93). MSCs are also recruited to the TME, where they secrete EVs that potentially suppress antitumor immunity, ultimately creating a favorable milieu for tumor progression (94). As a well-established anti-apoptotic and oncogenic miRNA, miR-21-5p serves not only as a prognostic marker for lung cancer (95), but also, when downregulated, promotes M1 macrophage polarization, thereby enhancing pro-inflammatory responses and anti-tumor immunity (96). A previous comparative study investigated the effects and mechanisms of exosomes derived from MSCs under normoxic (N-EV) and short-term hypoxic preconditioning (H-EV) conditions on NSCLC progression (97). The results demonstrated that exosomes derived from MSCs subjected to hypoxic preconditioning carry miR-21-5p, which targeted and reduced the expression of PTEN, programmed cell death 4 and reversion-inducing cysteine-rich protein with kazal motifs, consequently activating the Akt and STAT3 signaling pathways (97). This led to the increased expression of Arg-1, CD163, CD206, IL-10 and TGF- β , along with the decreased expression of CD86 and CD40, collectively promoting M2 macrophage polarization, while inhibiting M1 polarization; this polarization imbalance has significantly exacerbated the immunosuppressive state in the microenvironment of NSCLC, creating favorable conditions for tumor immune escape (97). Furthermore, H-EVs inhibited apoptosis in A549 and H23 cells, promoted their proliferation, invasion and migration, and increased N-cadherin and vimentin expression, thereby facilitating EMT. *In vivo* xenograft models further confirmed that H-EVs significantly increased Ki-67 and CD31 expression levels in tumor tissues, promoting tumor cell proliferation and angiogenesis, respectively (97). EVs serve as key mediators of intercellular communication, and the miRNAs they carry can be delivered to recipient cells, where they exert biological functions by regulating the expression of multiple target genes (98). Notably, the hypoxic state within the TME is not only a key driver of cancer growth and progression (99), but is also closely associated with immunosuppression (100). miR-103a is considered to participate in hypoxia-induced reprogramming within the TME, particularly in key processes, such as angiogenesis and immune editing (101). In this context, a previous study isolated EVs from human lung cancer CL1-5 cells and investigated the impact of hypoxic conditions on their functions. The expression of miR-103a in exosomes derived from lung cancer cells was significantly downregulated under hypoxic conditions, which targets and inhibits PTEN, leading to the activation of the PI3K/AKT and STAT3 signaling pathways (102). Given that PTEN is one of the most common inactivated tumor suppressor genes in lung cancer, its functional deficiency leads to the continuous activation of the PI3K/AKT pathway. Moreover, STAT3, as a key transcription factor for inflammation and immune regulation, is also frequently abnormally activated in lung cancer. The synergistic signal transduction of these two factors constitutes a core molecular event that drives the malignant progression of lung cancer and the remodeling of the immune microenvironment. This cascade increases the expression of Arg-1, IL-10, CCL18 and CCL22, thereby promoting M2 macrophage polarization (102). This polarization process significantly exacerbated the immunosuppressive

state in the lung cancer microenvironment, creating favorable conditions for tumor immune escape and malignant progression. Additionally, hypoxic EVs enhance the proliferation, invasion and migration of lung cancer cells, while upregulating the expression of VEGF-A and angiopoietin-1, thus promoting tumor angiogenesis (102). Long non-coding RNA small nucleolar RNA host gene 16 (SNHG16), a newly identified oncogene, has been shown to promote the progression of NSCLC (103). Kinesin family member 5A (KIF5A) has been characterized as an oncogene that promotes invasiveness in hepatocellular carcinoma, and its oncogenic role in LUAD has also been validated (104). miR-132-3p, which serves as a bridging molecule connecting SNHG16 and KIF5A, exhibits significant tumor-suppressive effects (96). As previously demonstrated, exosomes derived from hypoxic NSCLC cells carrying SNHG16 (SNHG16-EVs) downregulate miR-132-3p expression, leading to the upregulation of KIF5A. This cascade increases the expression of CD163, CD206 and Arg-1, thereby promoting M2 macrophage polarization; this polarization process further exacerbates the immunosuppressive microenvironment of NSCLC. Additionally, it enhances the expression of stemness markers, SOX2, OCT4 and Nanog, thereby strengthening the stemness of A549 and H1299 cells. Since tumor stem cells are closely associated with drug resistance, recurrence and metastasis in NSCLC, their enhanced stemness confers stronger self-renewal capabilities and treatment resistance to tumor cells. Moreover, it increases N-cadherin and vimentin expression, while decreasing E-cadherin expression, thereby inducing EMT (60). Furthermore, it upregulates cyclin-dependent kinase (CDK)2, CDK4 and CDK6 levels, accelerating cell cycle progression (60). Given that CDK2/4/6 are the core regulatory factors for the G1/S phase transition, their abnormal high expression in NSCLC drives the rapid proliferation of tumor cells and is an important molecular basis for the malignant progression of lung cancer. Radiotherapy is one of the primary treatment modalities for NSCLC, with >50% of patients receiving radiotherapy to achieve local tumor control, symptom relief, or disease stabilization (105). However, resistance to radiotherapy is a significant challenge that limits its clinical efficacy. Moreover, immune cells within the TME, particularly TAMs, play a crucial role in mediating radiotherapy resistance. miR-616-3p has been reported to be aberrantly expressed in various malignancies, including gastric, breast and colon cancers (106). PTEN plays a critical role in regulating macrophage polarization, and it is one of the most common inactivated tumor suppressor genes in NSCLC. Its functional deficiency leads to the continuous activation of the PI3K/AKT pathway (107). The PTEN/PI3K/AKT signaling pathway is also key to both macrophage polarization and the progression of NSCLC, and the abnormal activation of this pathway is closely related to cell survival, proliferation and the establishment of an immunosuppressive microenvironment in NSCLC, and constitutes a core molecular event driving the progression of malignancy (108). miR-616-3p expression is upregulated in NSCLC tissues and is further elevated following radiotherapy, potentially contributing to radiotherapy resistance by influencing macrophage polarization, this polarization process not only exacerbates the immunosuppressive microenvironment, but also directly weakens the cytotoxic effect of radiotherapy through paracrine mechanisms, ultimately

accelerating the malignant progression of NSCLC. Mechanistically, miR-616-3p in exosomes of NSCLC cells induced by radiotherapy can target and inhibit PTEN expression, upregulate the p-PI3K/PI3K and p-AKT/AKT ratios, and activate the PI3K/AKT signaling pathway. This subsequently increases the expression of M2 polarization markers, such as CD163, CD206, Arg-1, IL-10 and TGF- β 1, promoting macrophage polarization toward the M2 phenotype and ultimately accelerating the malignant progression of NSCLC. These findings suggest that the miR-616-3p/PTEN/PI3K/AKT axis induced by radiotherapy reprograms macrophages towards M2 polarization, establishing an immunosuppressive and survival-promoting microenvironment, thereby driving the radiotherapy resistance and malignant progression of NSCLC (109). Targeting this axis may provide a novel therapeutic strategy for overcoming resistance to radiotherapy (109). The activation of the programmed cell death protein 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) signaling axis suppresses T-cell-mediated immune responses (110). IFN- γ upregulates PD-L1 expression, and the overexpression of PD-L1 on the surface of tumor cells can induce the apoptosis of tumor-infiltrating T-cells, thereby inhibiting antitumor immunity (111). A previous study demonstrated that the expression of miR-708-5p in exosomes derived from LUAD cells was significantly upregulated, and this suggests that this miRNA may exert multiple regulatory effects in the LUAD microenvironment through exosome-mediated intercellular communication (112). Further investigations revealed that miR-708-5p targets and inhibits PTEN expression, increases the p-AKT/AKT and p-mTOR/mTOR ratios, and activates the AKT/mTOR signaling pathway, thereby upregulating the expression of M2 polarization markers, such as CD206, Arg-1 and IL-10, ultimately inducing macrophage polarization toward the M2 phenotype; this polarization process significantly exacerbated the immunosuppressive state in the microenvironment of LUAD. Concurrently, miR-708-5p induces PD-L1 transcription and translation, enhancing the proliferation, invasion and migration of H1299 cells, and promoting immune escape. Mechanistic analyses indicate that exosome-derived miR-708-5p stimulates IFN- γ production in T-cells, while concurrently inhibiting CD8⁺ T-cell function, exerting an immunomodulatory effect (112). Furthermore, in an Lewis lung cancer cells (LLCs) tumor transplantation model, miR-708-5p was confirmed to accelerate transplanted tumor growth by upregulating PD-L1 expression (112). The aforementioned results indicate that the miR-708-5p/PTEN/AKT/mTOR axis drives the oncogenic function of LUAD malignancy by simultaneously inducing M2-type macrophage polarization and upregulating PD-L1-mediated immune escape (112).

Regulation of macrophage polarization by long non-coding RNAs mediated by miRNAs. Cancer-associated fibroblasts (CAFs), as core components of the TME, promote tumor growth and metastasis through the secretion of exosomes (113). miR-335-5p plays an oncogenic role in NSCLC (114). The expression of CAF-derived LINC01833 is significantly upregulated in NSCLC tissues, and its high expression is closely associated with a poor patient prognosis; this suggests that it may play a key role as a carcinogenic factor in the progression of NSCLC (115). Vesicle-associated

membrane protein-associated protein A (VAPA) is involved in intracellular transport and microtubule-related processes, and its dysregulation can lead to cellular dysfunction (116). Mechanistic study has revealed that LINC01833 downregulates miR-335-5p expression, leading to upregulation of VAPA. This cascade reduces the expression of iNOS and CXCL9, while increasing the expression of Arg-1, CCL22, and CD206, thereby promoting M2 macrophage polarization and inhibiting M1 polarization; this polarization significantly exacerbates the immunosuppressive state in the microenvironment of NSCLC. Consequently, it enhances the proliferation, invasion, and migration of NSCLC cells (117). The aforementioned findings indicate that the LINC01833/miR-335-5p/VAPA axis derived from CAFs reprograms macrophages to the M2 phenotype and directly promotes the malignant behavior of tumor cells, playing a dual oncogenic role in the progression of NSCLC. Recent studies have demonstrated that the high expression of the long non-coding RNA LINC00313 is significantly associated with a poor prognosis of patients with cancer, suggesting its role as a pro-tumorigenic factor that drives tumor progression (118,119). Conversely, miR-135a-3p functions as a tumor suppressor (120). STAT6 is the core transcription factor of the IL-4/IL-13 signaling pathway. Its activation serves as a key molecular switch that drives the polarization of M2-type macrophages. In the lung cancer microenvironment, the abnormal activation of STAT6 can induce the transcription of a series of immunosuppressive factors, thereby promoting tumor immune escape (121). Research has revealed that LINC00313 can function as a ceRNA sponge-like molecule that binds to miR-135a-3p to upregulate STAT6 expression, leading to the increased expression of M2-associated markers, such as CD206, CD163, found in inflammatory zone 1 (Fizz1) and TGF- β , thereby promoting M2 macrophage polarization. Concurrently, it reduces the expression of M1-associated markers including CD86, iNOS, TNF- α and IL-1 β , inhibiting M1 macrophage polarization; this polarization process significantly exacerbates the immunosuppressive state in the lung cancer microenvironment. Additionally, LINC00313 promotes the proliferation, invasion and migration of A549, NCI-H1299 and H1975 cells (121). Results from *in vivo* xenograft models are highly consistent with *in vitro* findings, further confirming the central pro-tumorigenic role of LINC00313, and this indicates that the LINC00313/miR-135a-3p/STAT6 axis reprograms macrophages to the M2 phenotype through reprogramming and directly promotes the malignant behavior of lung cancer cells, thereby exerting a dual carcinogenic function (121).

Regulation of macrophage polarization by circular RNA (circRNA)-encoded miRNAs. The JAK/STAT3 pathway plays a critical regulatory role in tumor development and macrophage polarization. In LUAD, the continuous phosphorylation activation of STAT3 is one of the key molecular events that drive the malignant progression of the tumor (such as lymphatic metastasis). A study has shown that IGF2BP3 can stabilize SRC mRNA through m⁶A-dependent mechanisms, thereby triggering the activation of the STAT3 pathway and exerting a carcinogenic effect in lung cancer. Its abnormal high expression is closely related to poor patient prognosis (122). circRNAs, as a distinct class of non-coding RNA molecules, exhibit differential expression between LUAD tissues and adjacent normal tissues, and play critical

roles in tumor proliferation, metastasis and prognosis (123). For instance, circ_0001715 promotes the growth and metastasis of NSCLC cells by regulating the miR-1249-3p/FGF5 signaling axis (124). Moreover, miR-205-5p functions as a tumor suppressor in various types of cancer, and its deficiency or dysfunction significantly accelerates the malignant progression of lung cancer (125). Further research has revealed that circ_0001715 directly targets miR-205-5p, leading to triggering receptor expressed on myeloid cells-2 upregulation and the increased expression of M2-associated markers, such as CD206, IL-10 and TGF- β , thereby promoting M2 macrophage polarization (126). Concurrently, it reduces the expression of M1-associated markers including CD86, TNF- α and iNOS, inhibiting M1 macrophage polarization; this polarization process significantly exacerbates the immunosuppressive state in the microenvironment of LUAD. Moreover, circ_0001715 significantly enhances the proliferation, invasion and migration of A549 and H1975 cells (126). These results indicate that the circ_0001715/miR-205-5p/IGF2BP3/JAK-STAT3 axis reprograms the polarization balance of macrophages and directly promotes the malignant phenotype of LUAD cells, exerting a dual carcinogenic effect (126). Matrix metalloproteinase (MMP)14, a key member of the MMP family, has been shown to promote cancer cell migration and invasion, thereby accelerating malignant tumor progression. In lung cancer, MMP14 can promote tumor infiltration and metastasis through multiple mechanisms such as degrading the extracellular matrix (ECM), releasing growth factors, and activating other members of the MMP family (127). miR-1287-5p functions as a tumor suppressor in various malignancies, and its dysregulation is closely associated with tumor initiation and progression (128). A previous study revealed that MMP14 expression levels were significantly negatively associated with the overall survival of patients with LUAD; this indicates that MMP14 is a key negative regulatory factor for the prognosis of LUAD (129). Further mechanistic investigations demonstrated that circ-ADRM1 functioned as a ceRNA sponge-like molecule that binds to miR-1287-5p and recruited the deubiquitinating enzyme USP12, synergistically upregulating MMP14 expression. This led to the increased expression of M2-associated markers such as CD206, Arg-1, peroxisome proliferator-activated receptor (PPAR)G and Fizz1, thereby promoting M2 macrophage polarization; this further exacerbated the immunosuppressive state mediated by M2-type TAMs in the LUAD microenvironment (129). Additionally, circ-ADRM1 enhanced the proliferation, invasion and migration of A549, PC-9, H1975, H1435 and H2030 cells. The aforementioned results indicate that the circ-ADRM1/miR-1287-5p/USP12/MMP14 axis synergistically promotes the malignant progression of LUAD through multiple mechanisms, including promoting ECM degradation, driving M2 polarization of macrophages, and directly enhancing the malignant phenotype of tumor cells (129).

Regulation of macrophage polarization by miRNAs mediated by other factors. Cypermethrin (CYM) exhibits estrogen receptor activity and has been shown to induce cell proliferation and promote tumor metastasis (130). Previous research has demonstrated that the upregulation of miR-155 promotes M1 macrophage polarization (131). The upregulation of Bcl6 expression can promote immunosuppressive signals,

and the inhibition of the JNK pathway is closely related to the remodeling of the immune microenvironment in lung cancer. CYM can downregulate miR-155 expression, leading to the upregulation of Bcl6 and the subsequent downregulation of mitogen-activated protein kinase 4 (MKK4), which in turn inhibits the JNK signaling pathway. This cascade results in the decreased expression of TNF- α , IL-1 β , and iNOS, along with the increased expression of Arg-1, Fizz1 and macrophage galactose N-acetyl-galactosamine specific lectin, thereby promoting M2 macrophage polarization, while inhibiting M1 polarization; this polarization significantly exacerbates the immunosuppressive state in the lung cancer microenvironment. Additionally, CYM upregulates the expression of MMP10, MMP9, and CCL7, thereby promoting the invasion and metastasis of LLCs. In lung cancer mouse models, CYM has been confirmed to drive TAMs toward the metastasis-promoting M2 phenotype and significantly increase the number of lung metastases (132). The aforementioned results indicate that CYM reprograms the imbalance of macrophage polarization through the miR-155/Bcl6/MKK4/JNK axis, upregulates invasion-related molecules and strengthens the immunosuppressive microenvironment, thereby synergistically driving the invasion and metastasis of lung cancer (132). Misshapen-like kinase 1 (MINK1) has been identified as an activator of the JNK pathway (133), which is associated with M2 macrophage polarization (134). miR-3153 is differentially expressed in the plasma of patients with NSCLC; this suggests that it may serve as a diagnostic or prognostic biomarker and be involved in the progression of the disease (135). It has been demonstrated that the upregulation of miR-3153 activates the JNK signaling pathway by targeting and enhancing MINK1 expression, leading to the increased expression of M2 polarization markers, such as CD206, Arg-1, IL-10 and CCL2, thereby promoting M2 macrophage polarization, further exacerbating the immunosuppressive microenvironment in NSCLC. Additionally, miR-3153 upregulation enhances the proliferation, invasion, and migration of A549 and Calu3 cells. In mouse models, elevated miR-3153 expression significantly promotes tumor growth (136). The aforementioned results indicate that the miR-3153/MINK1/JNK axis promotes the polarization of macrophages towards a tumor-promoting M2 phenotype through coordinated reprogramming and directly enhances the malignant behavior of tumor cells, thereby driving the malignant progression of NSCLC (136). miR-10b expression is significantly upregulated in NSCLC tissues compared with adjacent normal tissues; this suggests that it may play a crucial role in promoting cancer development and progression in NSCLC (137). Further research has revealed that miR-10b promotes M2 macrophage polarization, as evidenced by increased expression of CD206, CD209, Arg-1, TNF- α , IL-6, IL-10, and TGF- β . Additionally, miR-10b enhances the proliferation, invasion, and migration of A549, NCI-H1650, and NCI-H1299 cells. Moreover, it increases N-cadherin expression, while decreasing E-cadherin expression, thereby inducing EMT (138). The aforementioned results indicate that miR-10b in NSCLC promotes cancer development by reprogramming macrophages to the M2 phenotype and inducing EMT transformation in tumor cells, exerting a dual carcinogenic effect (138). Within the TME, miR-146a has been shown to promote M2 macrophage polarization, thereby exerting

tumor-promoting effects (139,140). TNF receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK1) play a central role in promoting M1-type polarization and antitumor immune responses. It has been revealed that the upregulation of miR-146a targets and downregulates TRAF6 and IRAK1, leading to the increased expression of M2-associated markers, such as CD206, IL-10, and TGF- β , which promotes M2 macrophage polarization; this polarization process significantly exacerbated the immunosuppressive state in the lung cancer microenvironment. Conversely, it reduces CD86 expression, inhibiting M1 macrophage polarization (141). Additionally, miR-146a suppresses apoptosis of H1299 cells, while enhancing their proliferative, invasive and migratory abilities. These results indicate that miR-146a in lung cancer exerts a synergistic carcinogenic effect by inhibiting the TRAF6/IRAK1-mediated M1 polarization signal, reprogramming macrophages to the M2 phenotype, and directly promoting the survival and malignant behavior of tumor cells (141). The mechanisms by which miRNAs regulate macrophage polarization in lung cancer are summarized in Table I.

6. Synopsis

The prevention and treatment of lung cancer remain major research challenges, and the occurrence and progression of this malignancy are closely linked to macrophage polarization. Regulating the balance between M1 and M2 polarization has thus emerged as a key intervention strategy. Various miRNAs modulate the polarization balance of macrophages through alterations in their own expression and exert anti-lung cancer effects via multi-targeted synergistic mechanisms. Through summarization and analysis, it was found that:

i) As regards macrophage polarization and changes in miRNA expression, the upregulation of miR-99b (64), miR-let-7b-5p (68), miR-135a-5p (72), miR-770 (75) and miR-613 (77) promotes M1 polarization, while inhibiting M2 polarization. By contrast, the upregulation of miR-106a-5p (81), miR-21-5p (97), miR-3153 (136) and miR-146a (141), as well as the downregulation of miR-335-5p (117), miR-4319 (92), miR-103a (102), miR-155 (132) and miR-132-3p (60), inhibits M1 polarization and promotes M2 polarization. The underlying basis for these differential effects lies in the specificity of target genes and signaling pathways, and their realization is regulated by cell type specificity, temporally specific expression, and local microenvironmental signals. In terms of the specificity of target genes and signaling pathways, miRNAs can regulate different polarization directions through specific targets. For instance, in M1-type macrophages activated by TLR4, miR-155 negatively regulates the negative regulatory factors of signaling pathways, such as SHIP1 and SOCS1, thereby promoting M1 polarization. However, in M2 polarization induced by IL-4, the expression pattern of miR-155 is completely opposite to that observed in M1: miR-155 is significantly upregulated in M1 polarization, whereas its expression remains largely unchanged or mildly decreased in M2 polarization. This opposite regulatory direction suggests that the function of miR-155 is highly dependent on the specific activated signaling pathways and target gene networks involved (142). The time-specific expression is manifested in

the temporal regulation of macrophage polarization process by miRNAs. During the 8-h dynamic process of bone marrow-derived macrophages polarizing into the M1 type, M1-related miRNAs can be classified into the early response group and late response group based on the sequence of their expression peaks. Among these, miR-1931, miR-3473e and miR-5128 have been verified as early response miRNAs, suggesting that they play a key regulatory role in the initiation stage of polarization (143). Furthermore, the target sites of miR-155 in activated macrophages, dendritic cells and B-cells are ~20 to 75% cell-specific. This specificity persists in the co-expression of miR-155 with its targets SOCS1 and SHIP1, which exhibited a coordinated expression in single macrophages and tissue niches, reflecting fine-tuning rather than binary regulation. This difference is not due to the variable polyadenylation of the 3'UTR, but is determined by the intrinsic cellular environment (such as transcription factors, chromatin state) (144).

ii) Signaling pathway regulation exhibits distinct patterns. miRNAs regulate the polarization state of macrophages by targeting multiple key signaling pathways, thereby influencing the progression and prognosis of lung cancer. According to the existing literature, these pathways mainly involve the NF- κ B pathway, the PTEN/PI3K/AKT pathway, the MAPK pathway and the JAK/STAT pathway, etc. The regulatory patterns of each pathway exhibit certain regular characteristics. Among these, the PTEN/PI3K/AKT pathway is the core hub for miRNA to regulate M2 polarization, and it is particularly crucial in hypoxic microenvironments. The NF- κ B and PI3K/AKT pathways are predominantly activated, whereas the MAPK pathway is generally inhibited. Notably, the JNK and STAT-related pathways exert dual regulatory effects. For instance, miR-155 downregulation inhibits JNK (132), while miR-3153 upregulation activates it (136); both promote M2 polarization and lung cancer progression. Similarly, the upregulation of miR-106a-5p (81), miR-21-5p (97), miR-1290 (84) and miR-214-3p (89), along with the downregulation of miR-103a (102), activates STAT pathways, favoring M2 polarization and tumor progression. By contrast, the upregulation of miR-135a-5p (72) inhibits the STAT6/GATA3/IL-4 axis, suppressing M2 polarization and exerting an anti-lung cancer effect. The differential regulatory effects of these pathways may be attributed to factors, such as the specificity of target genes and signaling pathways, cell type and microenvironment dependence, distinct nodal points within the pathways, as well as the dose effects and the network balance of gene expression. These pathways do not exist independently, but are intertwined to form a complex regulatory network. Microenvironmental factors, such as hypoxia and inflammation can significantly affect the activity of these pathways, thereby altering the regulatory direction of miRNAs. Specifically, lung cancer cells release EVs containing miR-20a-5p under hypoxic conditions, which can target and inhibit PTEN, activate AKT, and promote M2 phenotypic polarization (145). Additionally, lung adenocarcinoma M2 macrophages highly express AQP3. Through the PPAR- γ /NF- κ B axis, they promote M2 polarization and upregulate IL-6, thereby affecting tumor growth and migration (146). Future research is required to further clarify the interactions among these pathways and their specificity in

Table I. Summary of the mechanisms of the regulation of macrophage polarization in lung cancer by miRNAs.

Regulator	miRNA	Expression change	Direct targets and changes	Lung cancer study model	Regulation of macrophage polarization	Effect on lung cancer	(Refs.)
Unspecified	miR-99b	Upregulation	NF-κB, mTOR ↓	Lung cancer subcutaneous tumor model	Promote M1 polarization; Inhibit M2 polarization	Suppress lung cancer progression	(64)
Unspecified	miR-let-7b-5p	Unspecified	AP1S1 ↓	A549 and H1299 cells	Promote M1 polarization; Inhibit M2 polarization	Suppress lung cancer progression	(68)
Unspecified	miR-135a-5p	Upregulation	Unspecified	A549, H1299 and H460 cells	Promote M2 polarization; Inhibit M1 polarization	Suppress lung cancer progression	(72)
Unspecified	miR-770	Upregulation	MAPK ↓	K-MES-1, A549 and NCI-H1650 cells; transgenic mouse model for xenotransplantation	Promote M1 polarization; Inhibit M2 polarization	Suppress lung cancer progression	(75)
Unspecified	miR-613	Upregulation	Unspecified	NSCLC patients; A549, HCC827, H1299 and H1650 cells	Promote M1 polarization; Inhibit M2 polarization	Suppress lung cancer progression	(77)
Intermittent hypoxia (IH)	miR-106a-5p	Upregulation	PTEN ↓	NSCLC and OSAS patients; Tumor xenograft model of nude mouse; A549 and NCI-H226 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(81)
Unspecified	miR-1290	Unspecified	SOC3 ↓	A549 and H1299 cells; Tumor xenograft model of nude mouse	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(84)
Unspecified	miR-21	Unspecified	IRF1 ↓	NSCLC patients; H1299 cells; Subcutaneous tumor mouse model	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(87)
hsa_circ_0051799	miR-214-3p	Unspecified	IGF2BP3 ↑	A549, PC-9, H1975 and H1395 cells; Tumor xenograft model of nude mouse	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(89)
GNAS-AS1	miR-4319	Downregulation	NECAB3 ↓	NSCLC patients; A549 and H1299 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(92)
Hypoxia-preconditioned MSCs-EVs	miR-21-5p	Upregulation	PTEN, PDCD4, RECK ↓	A549 and H23 cells; tumor xenograft model of nude mouse	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(97)
Hypoxic EVs	miR-103a	Downregulation	PTEN ↓	CL1-5 cells; NCI-H2087, NCI-H1792 and NCI-H1437	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(102)

Table I. Continued.

Regulator	miRNA	Expression change	Direct targets and changes	Lung cancer study model	Regulation of macrophage polarization	Effect on lung cancer	(Refs.)
Oxygen-deficient NSCLC cell-derived SNHG16-EVs	miR-132-3p	Downregulation	KIF5A ↑	NSCLC patients; A549 and H1299 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(60)
Unspecified	miR-616-3p	Unspecified	PTEN ↓	NSCLC and OSAS patients; A549 and H1299 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(109)
Unspecified	miR-708-5p	Unspecified	PTEN ↓	A549, H1299 and H358 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(112)
LINC01833	miR-335-5p	Downregulation	VAPA ↑	NSCLC patients; Tumor xenograft model of nude mouse	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(117)
LINC00313	miR-135a-3p	Upregulation	STAT ↑	A549, NCI-H1299 and H1975 cells; Tumor xenograft model of nude mouse	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(121)
circ_0001715	miR-205-5p	Unspecified	TREM2 ↑	A549 and H1975 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(126)
Circ-ADRM1	miR-1287-5p	Unspecified	MMP14 ↑	A549, PC-9, H1975, H1435 and H2030 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(129)
CYM	miR-155	Downregulation	Bcl6 ↑	LLCs	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(132)
Unspecified	miR-3153	Upregulation	MINK1 ↑	LUAD patients; A549 and Calu3 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(136)
Unspecified	miR-10b	Unspecified	Unspecified	A549, NCI-H1650 and NCI-H1299 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(137)
Unspecified	miR-146a	Upregulation	TRAF-6, IRAK-1 ↓	H1299 cells	Promote M2 polarization; Inhibit M1 polarization	Drive lung cancer progression	(141)

Upward arrows (↑) indicate an increase/enhancement, while downward arrows (↓) indicate a decrease/inhibition. API51, adaptor-related protein complex 1 subunit sigma 1; PTEN, phosphatase and tensin homolog; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; IRF1, interferon regulatory factor 1; NECAB3, N-terminal EF-hand type calcium-binding protein 3; PDCD4, programmed cell death 4; RECK, reversion-inducing cysteine-rich protein with kazal motifs; KIF5A, kinesin family member 5A; VAPA, vesicle-associated membrane protein-associated protein A; TREM2, triggering receptor expressed on myeloid cells 2; MMP14, matrix metalloproteinase 14; MINK1, misshapen-like kinase 1; TRAF6, TNF receptor-associated factor 6; IRAK1, interleukin-1 receptor-associated kinase 1.

different stages and subtypes of lung cancer, providing a theoretical basis for targeted precision treatment of imbalanced macrophage polarization.

iii) As regards the regulatory coordination mechanisms, the main aspects involved include proliferation, invasion and migration (64,68,72,77,81,84,87,92,97,102,109,112,117,121,126,129,132,136,138,141), apoptosis (75,77,141), angiogenesis (97,102), cell cycle regulation (60), maintenance of stemness (60) and EMT (60,68,81,97,138). Among these, studies on proliferation, invasion and migration, EMT and apoptosis are more prevalent, whereas investigations into angiogenesis, cell cycle regulation, and cancer stemness are relatively limited. To date, there have been no systematic reports in the literature regarding miRNAs regulating iron death or disulfide bond death, which are novel forms of cell death, by modulating macrophage polarization, thereby influencing the complete regulatory network of the malignant progression of lung cancer. The observed heterogeneity in the focus of these coordinated regulatory mechanisms may be closely related to limitations in existing model systems and detection methods, inconsistencies in the depth of mechanistic interpretation across different phenotypes, and potential biases in target recognition during functional screening. For instance, in the TME of commonly used mouse models, the infiltration of T-cells is significantly lower than that in human tumors, while the density of macrophages is abnormally high (147). Additionally, two-dimensional co-culture or tumor organoid models often fail to accurately reflect the complex regulatory environment of multiple factors in the body due to the lack of complete immune cell components (148). More importantly, genome-wide CRISPR screening relies on *in vitro* immortalization or bone marrow-derived macrophages, whose genetic epigenetic states are different from those of primary TAMs (149). This makes it prone to screening out targets whose functions are masked or compensated *in vivo*, resulting in clinical transformation deviations.

iv) Research depth varies significantly across miRNAs. The most extensive studies, i.e., those covering cellular, animal and clinical levels, are available for miR-106a-5p and miR-21. miR-616-3p, miR-3153, miR-4319 and miR-132-3p have been validated in both cellular systems and clinical samples. miR-1290, miR-214-3p and miR-770 have been examined in cell-based assays and xenograft models. In contrast, most other miRNAs (e.g., miR-let-7b-5p, miR-155) remain at the cellular stage. These substantial differences in research depth may be attributed to factors, such as the expression abundance of individual miRNAs, the difficulty of detection in clinical samples, the extent to which their potential as therapeutic targets drives research investment, the accessibility of sample types and the feasibility of establishing corresponding animal models. It is worth noting that the current research methodology has certain limitations. In terms of cell experiments, monolayer culture lacks the three-dimensional spatial structure and complete components of the tumor microenvironment (immune cells, CAFs, vascular endothelial cells and the cytokine network), making it difficult to assess the immune killing effect (150). In terms of animal models, species differences lead to fundamental differences in immunity, metabolism and pharmacokinetics between mice and humans, resulting in deviations in result transformation; at the same time, subcutaneous

transplanted tumors, orthotopic transplanted tumors, chemical induction models, and genetically engineered mice all have a disconnection from the natural occurrence and progression process of lung cancer, restricting the clinical translatability of the results (151).

v) In the hypoxic TME, the expression of multiple miRNAs becomes dysregulated, collectively exerting pro-tumorigenic effects on lung cancer by modulating macrophage polarization. Specifically, under hypoxic conditions, the expression of miR-106a-5p and miR-21-5p is upregulated, whereas the expression of miR-103a, miR-132-3p, miR-1290, miR-21 and miR-214-3p is downregulated. These alterations promote M2 polarization, while inhibiting M1 polarization, thereby driving the malignant progression of lung cancer. Collectively, these findings suggest that hypoxia, as a hallmark feature of the lung cancer microenvironment, induces miRNA dysregulation, which in turn drives macrophage polarization toward the M2 phenotype. This process reshapes the tumor immune microenvironment, promotes angiogenesis and tumor invasion, and exacerbates local hypoxia, ultimately forming a closed-loop positive feedback regulatory network.

vi) A single miRNA can simultaneously intervene in multiple key aspects of tumor progression through its multi-targeting characteristics. For example, in terms of pro-tumorigenic synergy, the upregulation of miR-21-5p promotes proliferation, invasion, migration, angiogenesis and EMT, while inhibiting apoptosis (97); the downregulation of miR-103a enhances proliferation, invasion, migration and angiogenesis (102); miR-10b promotes proliferation, invasion and migration, while inducing EMT (138). In terms of tumor-suppressive synergy, miR-let-7b-5p (68) and the upregulation of miR-135a-5p (72) both inhibit proliferation, invasion, migration and EMT; the upregulation of miR-146a inhibits proliferation, invasion and migration, while promoting apoptosis (141); and the upregulation of miR-770 inhibits proliferation, invasion and migration, induces EMT, and promotes apoptosis (75). The diversity and complexity of these miRNA functions essentially reflect the comprehensive output presented by the miRNA regulatory network under specific temporal and spatial conditions, and this output is constrained by many factors. For instance, in terms of molecular target competition, in NSCLC, lncRNA MALAT1 has been proven to function as a ceRNA, directly binding to miR-206, thereby blocking the inhibitory effect of miR-206 on MCP-1 and promoting the occurrence of lung cancer (152). In terms of cellular plasticity, miR-146a can exert tumor-suppressing effects by inhibiting the NF- κ B pathway, and can also promote tumor progression by remodeling the functions of TAM through extracellular vesicles (153). Furthermore, in terms of dose-threshold effects, the bone marrow-derived macrophages of mice with miR-23a-27a-24-2 cluster knocked out showed a weakened inflammatory response (M1 type) upon lipopolysaccharide stimulation, while the M2 type response was enhanced; however, the overexpression of this cluster produces the opposite effect (154). In terms of upstream regulatory RNA networks, the main regulation is through circular RNAs acting as 'sponges' for miRNAs. In LUAD, circHIF1A acts as a sponge to absorb miR-486-5p, upregulating GRHL2, promoting the malignant phenotype of the tumor and inducing M2 polarization through IL-10 (155). This complexity also

suggests that when developing miRNA-based diagnostic markers or therapeutic agents, comprehensive analyses need to be conducted in the context of specific cellular backgrounds and lung cancer subtypes.

vii) In terms of regulatory targets, studies related to PTEN are relatively abundant. For example, miR-708-5p and miR-616-3p can downregulate PTEN expression; similarly, the downregulation of miR-106a-5p and miR-21-5p, as well as the upregulation of miR-103a, also target and inhibit PTEN expression, thereby inducing M2 polarization and promoting lung cancer progression. This may be attributed to PTEN serving as a central metabolic checkpoint in macrophage polarization, with its 3'UTR region rich in miRNA response elements, and to the functional redundancy and coordinated regulation among multiple miRNAs (156).

viii) Additionally, miR-135a-5p and miR-135a-3p both originate from different arms of the same precursor pre-miR-135a (namely the 5p arm and the 3p arm). However, the upregulation of miR-135a-5p can inhibit lung cancer, while the upregulation of miR-135a-3p may promote lung cancer. It is considered that this difference may be related to the preference of Dicer/AGO2 for the processing of the two arms, the cell type-specific regulatory mechanisms, changes in arm transformation or arm processing regulation, and the differences in the target gene networks of the two. The functions of miR-135a-5p and miR-135a-3p in lung cancer exhibit notable differences. Specifically, miR-135a-5p can promote the growth, migration and invasion of lung cancer cells by targeting and inhibiting LOXL4 (157). However, miR-135a-3p can target and inhibit the expression of KLF8, thereby exerting an anticancer effect (158). A more in-depth analysis of these mechanisms will help to comprehensively elucidate the complex regulatory network of miR-135a in lung cancer and provide a theoretical basis for precise intervention strategies based on miR-135a.

The current clinical translation of miRNA combination therapy still faces the following challenges: i) Low delivery efficiency: miRNAs are prone to degradation by nucleases in the body and difficult to achieve tumor-targeted delivery across biological barriers. For instance, a study on the targeted delivery of chemically modified miR-34a to prostate cancer clearly indicated that the clinical application of tumor suppressive miRNAs as anticancer drugs is constrained by three major bottlenecks: The lack of efficient delivery vectors, the capture of miRNAs in endocytic compartments preventing their release, and the rapid degradation of nucleases in the circulatory system (159). ii) Significant off-target effects: In the majority of cases, a single miRNA can regulate multiple target genes. Although this extensive regulatory function enables miRNAs to control various cellular processes, it also increases the possibility of off-target effects on non-target genes. Such off-target interactions may have harmful effects by interfering with normal cellular functions or initiating oncogenic signals (160). Therefore, how to effectively avoid the off-target effect has become one of the key challenges in the development of miRNA mimics and inhibitors. iii) Increased complexity of the treatment plan: This involves optimizing drug ratios, scheduling drug administration and considering drug interactions, which is more difficult than single-drug therapy. For example, a previous study on miRNA-targeted mesylate oligonucleotides (μ -ON) triad

combination (μ -21-ON/ μ -17-ON/ μ -155-ON) demonstrated that although this combination achieved a 4-fold delay in tumor growth in the mouse RLS40 lymphosarcoma model, its efficacy was highly dependent on precise drug ratio matching and administration sequence. The optimization of the treatment window was much more difficult than that of a single drug (161). iv) Increased risk of toxicity: Combined delivery may superimpose the adverse reactions of each component, leading to potential systemic toxicity increase. For instance, lipid nanoparticles, as a commonly used delivery carrier, can damage cell membranes and accumulate in organs such as the liver, causing hepatotoxicity and inflammation (162). These limitations suggest that breakthroughs are needed in carrier design, targeting optimization, and safety evaluation.

7. Conclusion and future prospects

The current research has the following shortcomings: i) Inconsistent reporting of miRNA expression changes. Some miRNAs in the studies, such as miR-let-7b-5p (68), miR-1290 (84), miR-21 (87), miR-616-3p (105), and miR-708-5p (112), did not clearly indicate upregulation or downregulation, reflecting temporal and spatial heterogeneity as well as the insufficient understanding of the complexity of miRNA functions. ii) Gaps in research breadth: Emerging cell death mechanisms (e.g., ferroptosis, disulfidptosis) remain underexplored, and the systematic analysis of lncRNA/circRNA-miRNA sponge networks is lacking. iii) Limited mechanistic depth: Overreliance on single-target studies hinders the understanding of multi-target coordination, and the bidirectional regulation of JNK/STAT pathways remains unclear. iv) Incomplete translational research chain: Clinical validation is largely confined to tissue specimens, with insufficient use of liquid biopsies. Some animal models used in research, such as miR-let-7b-5p (68), miR-1290 (84), miR-21 (87), miR-616-3p (109), and miR-708-5p (112), rarely employ *in situ*, transgenic or humanized immune systems. These systems can more effectively replicate the microenvironment of lung cancer. v) Insufficient dynamic analysis of the hypoxic microenvironment: The spatiotemporal dynamics of hypoxia and its interplay with acidic pH and metabolic competition in modulating the miRNA-macrophage axis require further investigations.

In light of current research limitations, future investigations are warranted to focus on the following aspects: First, the expansion from classical phenotypes to novel regulatory networks by systematically screening miRNAs involved in ferroptosis and disulfidptosis, and integrating lncRNA/circRNA-miRNA-mRNA axes to construct ceRNA maps associated with macrophage polarization. Second, to deepen mechanistic analysis using multi-omics and single-cell sequencing to reveal multi-dimensional interactions and functional specificity across macrophage subpopulations. Third, strengthen translational research by validating serum- or exosome-derived miRNA biomarkers in multicenter cohorts, and utilizing humanized mouse models to evaluate miRNA-based therapies combined with immune checkpoint inhibitors. Fourth, to adopt dynamic, three-dimensional culture systems to study spatiotemporal regulation of miRNAs and macrophage polarization under tumor-like conditions. Finally,

clarify subtype-specific regulatory rules based on lung cancer driver genes, and design multi-target combination regimens to overcome resistance and enhance therapeutic efficacy.

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Availability of data and materials

Not applicable.

Authors' contributions

ZY was involved in the literature search, data extraction and in the drafting of the manuscript. LJ conceived the study and revised the manuscript critically. Both authors have read and approved the final manuscript. Data authentication is not applicable.

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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