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Review article

Regulation and therapeutic potentials of microRNAs to non-small cell lung cancer

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ABSTRACT

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80%–85% of total cases and leading to millions of deaths worldwide. Drug resistance is the primary cause of treatment failure in NSCLC, which urges scientists to develop advanced approaches for NSCLC treatment. Among novel approaches, the miRNA-based method has emerged as a potential approach as it allows researchers to modulate target gene expression. Subsequently, cell behaviors are altered, which leads to the death and the depletion of cancer cells. It has been reported that miRNAs possess the capacity to regulate multiple genes that are involved in various signaling pathways, including the phosphoinositide 3-kinase, receptor tyrosine kinase/rat sarcoma virus/mitogen-activated protein kinase, wingless/integrated, retinoblastoma, p53, transforming growth factor β, and nuclear factor-kappa B pathways. Dysregulation of these signaling pathways in NSCLC results in abnormal cell proliferation, tissue invasion, and drug resistance while inhibiting apoptosis. Thus, understanding the roles of miRNAs in regulating these signaling pathways may enable the development of novel NSCLC treatment therapies. However, a comprehensive review of potential miRNAs in NSCLC treatment has been lacking. Therefore, this review aims to fill the gap by summarizing the up-to-date information on miRNAs regarding their targets, impact on cancer-associated pathways, and prospective outcomes in treating NSCLC. We also discuss current technologies for delivering miRNAs to the target cells, including virus-based, non-viral, and emerging extracellular vesicle-based delivery systems. This knowledge will support future studies to develop an innovative miRNA-based therapy and select a suitable carrier to treat NSCLC effectively.

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1. Introduction

Lung cancer is a severe health issue with abnormal lung cell growth [1]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, with a poor prognosis and the absence of a definitive cure [2]. Besides smoking and air pollution, genetic factors such as genetic mutations significantly contribute to the development of NSCLC [3–6]. Mutations in either proto-oncogenes or tumor suppressor genes can trigger cancer development [7–9]. Therefore, investigating the role of these genes and involved signaling pathways is essential to develop effective target therapies for NSCLC. In the past decades, scientists have discovered a wide range of mutant genes, many of which are components of cellular signaling pathways contributing to NSCLC development and progression. These pathways include the PI3K, RTK/RAS/MAPK, WNT, RB, p53, TGF-β, and NF-κB signaling pathways. Their functions in NSCLC formation are summarized in Table 1.

The current standard treatment approaches applied for NSCLC, depending on the stage, include (1) surgery (for stages I, II, and IIIA - with adjuvant systemic therapy when appropriate); (2) neoadjuvant chemotherapy and radiation, followed by surgery (for stage III); and (3) immunotherapy (for stages III and IV) [32–36]. For distant metastases (stage IV), target therapy and immunotherapy could be considered for a specific driver mutation [32–36]. Surgical resection is typically the first choice and could effectively cure NSCLC patients in stages I and II; however, the recurrence rate after surgery is relatively high (ranging from 30% to 55%) [37,38]. Likewise, although chemo and radiotherapy may effectively inhibit cancer progression, they still have many side effects, such as sickness, hair loss, and diarrhea [39–41]. These conventional approaches not only damage cancer cells but also destroy healthy cells. Additionally, previous studies have revealed that malignant tumors could resist chemo-radiotherapy, resulting in more aggressive cancer progression [42–45]. Therefore, discovering novel therapies that could overcome these drawbacks is necessary to improve the treatment efficiency and survival rate of NSCLC patients [46–48].

Previous studies have shown that mutations in either proto-oncogenes or tumor suppressor genes can lead to cancer development; thus, developing therapy targeting mutated genes could effectively cure cancer [8,10,48–50]. In fact, thousands of studies have been conducted to evaluate the efficacy and safety of novel gene therapies, such as gene transfer, gene silencing, gene editing, oncolytic virotherapy, and immunotherapy [51–53]. Among those, the RNA interference (RNAi) strategy has drawn the attention of scientists due to its ability to target specific mRNAs without immunogenicity and low toxicity [54,55]. Between two types of small non-coding RNA (siRNAs and miRNAs), miRNAs could target multiple mRNAs simultaneously, which makes them powerful at modulating multiple disease pathways [56–59].

MicroRNAs (miRNAs) are small non-coding RNAs with 18–25 nucleotides in length [56,58,59]. Their therapeutic effects rely on their capacity to bind to specific sequences on targeted mRNAs, thereby modulating post-transcriptional processes in different manners [60,61]. To be more specific, miRNAs bind to the 3′ untranslated region (3′ UTR) of targeted mRNAs encoding for proteins involved in cancer-related signaling pathways. This binding results in the inhibition of proliferation, metastasis, invasion, and angiogenesis, the induction of apoptosis, and the enhancement of chemo-radio sensitivity of NSCLC cells [62–64]. Compared with other gene therapy strategies, miRNAs are more advanced and biosafe. They only impact the post-transcriptional regulation of target genes, thereby minimizing the potential risk of tumorigenesis associated with off-target gene integration or unwanted immune system responses [53, 65]. Furthermore, miRNAs' delivery efficiency and targeting ability could be significantly increased thanks to the application of advanced nanotechnologies in miRNA carriers [66–68]. For instance, MRX34, a liposome formulation of miR-34a, had been introduced to clinical trial in humans (ClinicalTrials.gov identifier: NCT01829971) due to its capacity to significantly reduce cell proliferation, migration, and invasion in various cancer types, such as liver cancer [69], head and neck squamous carcinoma, thyroid cancer [70], and melanoma [71]. Additionally, Targomir drug, which comprises synthetic miR-16 mimics encapsulated by a bacterial minicell system, has also entered clinical trials for treating thoracic cancer [72]. These clinical trials serve as compelling evidence of the potential utility of miRNAs in cancer treatment, not only for the aforementioned cancer types but also for NSCLC. In this review, we highlight miRNAs targeting NSCLC tissue and insights into their targets and delivery systems to devise innovative strategies for NSCLC treatment.

2. MiRNAs as therapeutic agents for NSCLC

As mentioned above, miRNAs can serve as either oncogenic agents or tumor suppressors depending on the proteins encoded by their target mRNAs [73]. Thus, miRNA expression is tightly associated with cancer-associated signaling pathways and understanding the complex interplay between miRNAs and their target pathways could help researchers design more effective miRNA-based drugs to combat NSCLC.

Table 1
Signaling pathways contribute to NSCLC development and progression.

Pathway	Proliferation	Apoptosis	Metastasis	Invasion	Angiogenesis	Chemoresistance	**References**
PI3K	Promote	Inhibit	Promote	Promote	Promote	Promote	[10–12]
RTK/RAS/MAPK	Promote	Inhibit	Promote	Promote	–	Promote	[13,14]
WNT	Promote	Inhibit	Promote	Promote	–	Promote	[15–21]
RB	Inhibit	Promote	–	–	–	–	[22]
p53	Dual role	Dual role	Dual role	Dual role	–	Dual role	[23,24]
TGF-β	Dual role	Dual role	Promote	Promote	Promote	–	[25–28]
NF-κB	Dual role	Dual role	Promote	Promote	–	Promote	[29–31]

PI3K Signaling Pathway
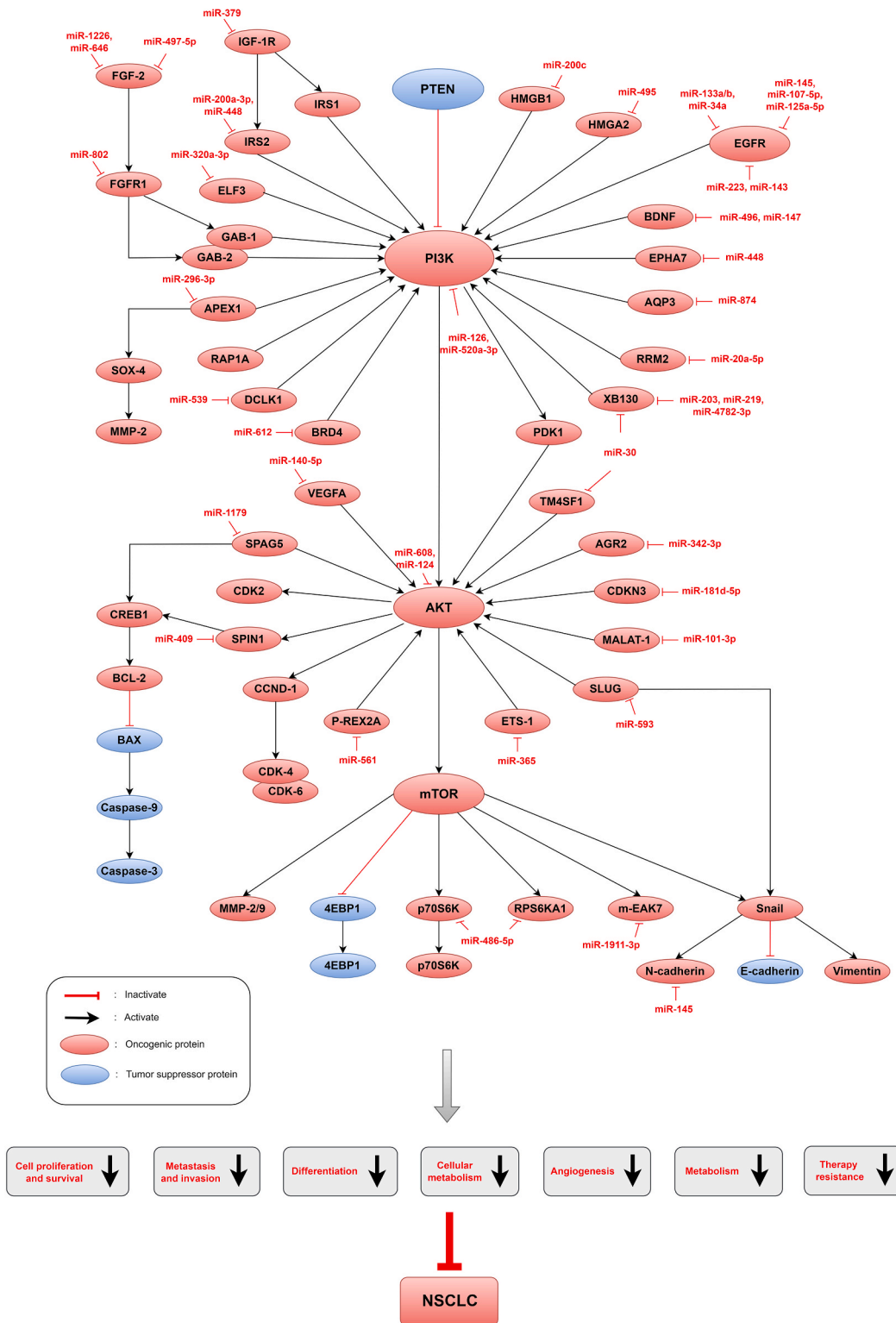
(caption on next page)

Fig. 1. Therapeutic targets and prospective outcomes of miRNAs modulating the PI3K pathway in NSCLC treatment. Legend: These miRNAs downregulate the expression of key oncogenes, such as EGFR, PI3K, AKT, mTOR, and their downstream genes within the PI3K pathway, leading to the inhibition of cell proliferation, metastasis, invasion, and angiogenesis while promoting apoptosis of NSCLC [49,57,77,79,80,84–121].
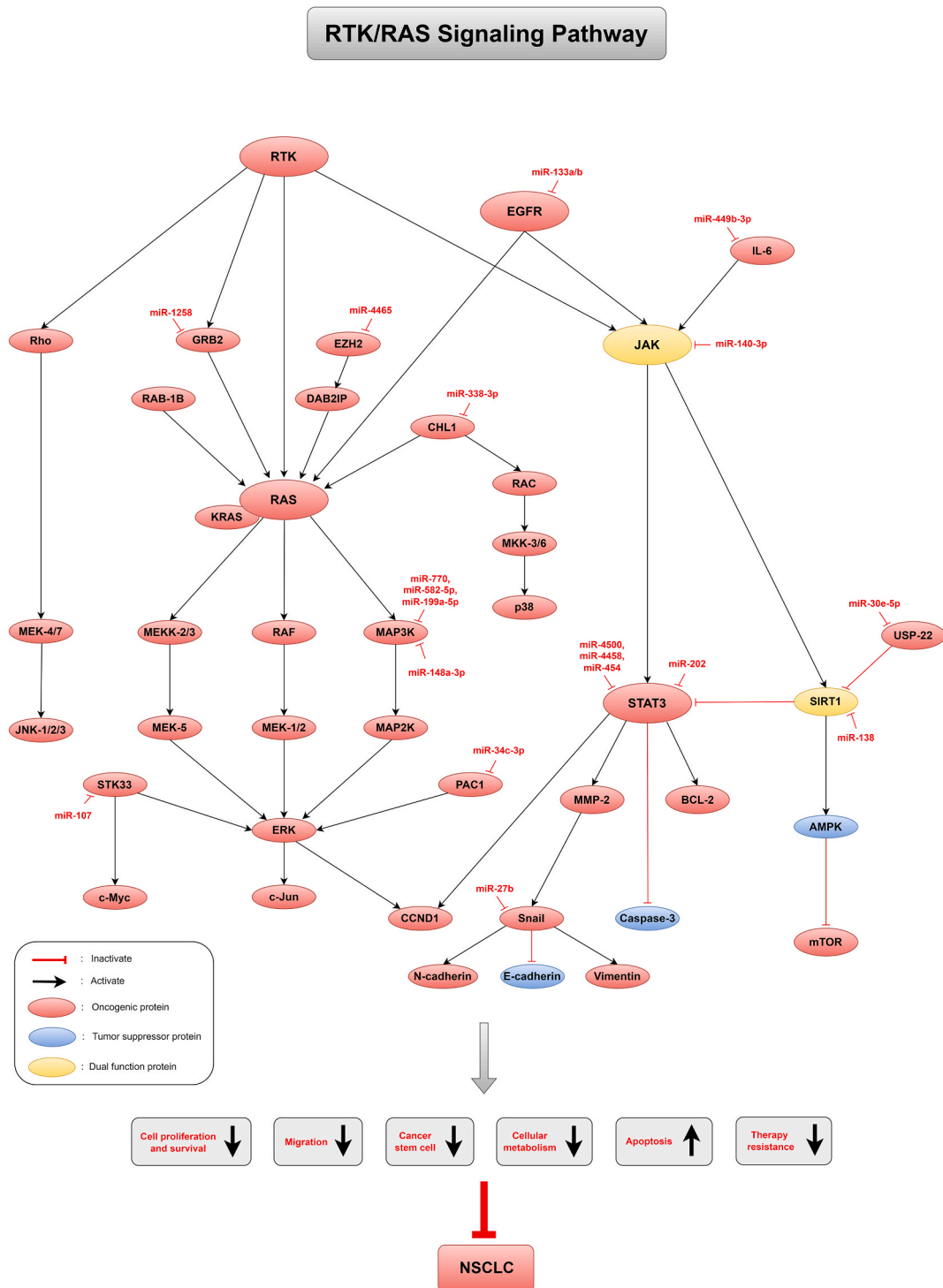

Fig. 2. miRNA-mediated silencing of oncogenes in the RTK/RAS/MAPK signaling pathway for NSCLC treatment. Legend: Aberrant activation of the RTK/RAS/MAPK signaling pathway can lead to NSCLC formation. However, these tumor suppressor miRNAs targeting oncogenic mRNAs within this pathway, like mRNAs of EGFR, STAT, and MAPK, robustly suppresses NSCLC proliferation, metastasis, invasion, and chemoresistance [127,128, 129,130–144].
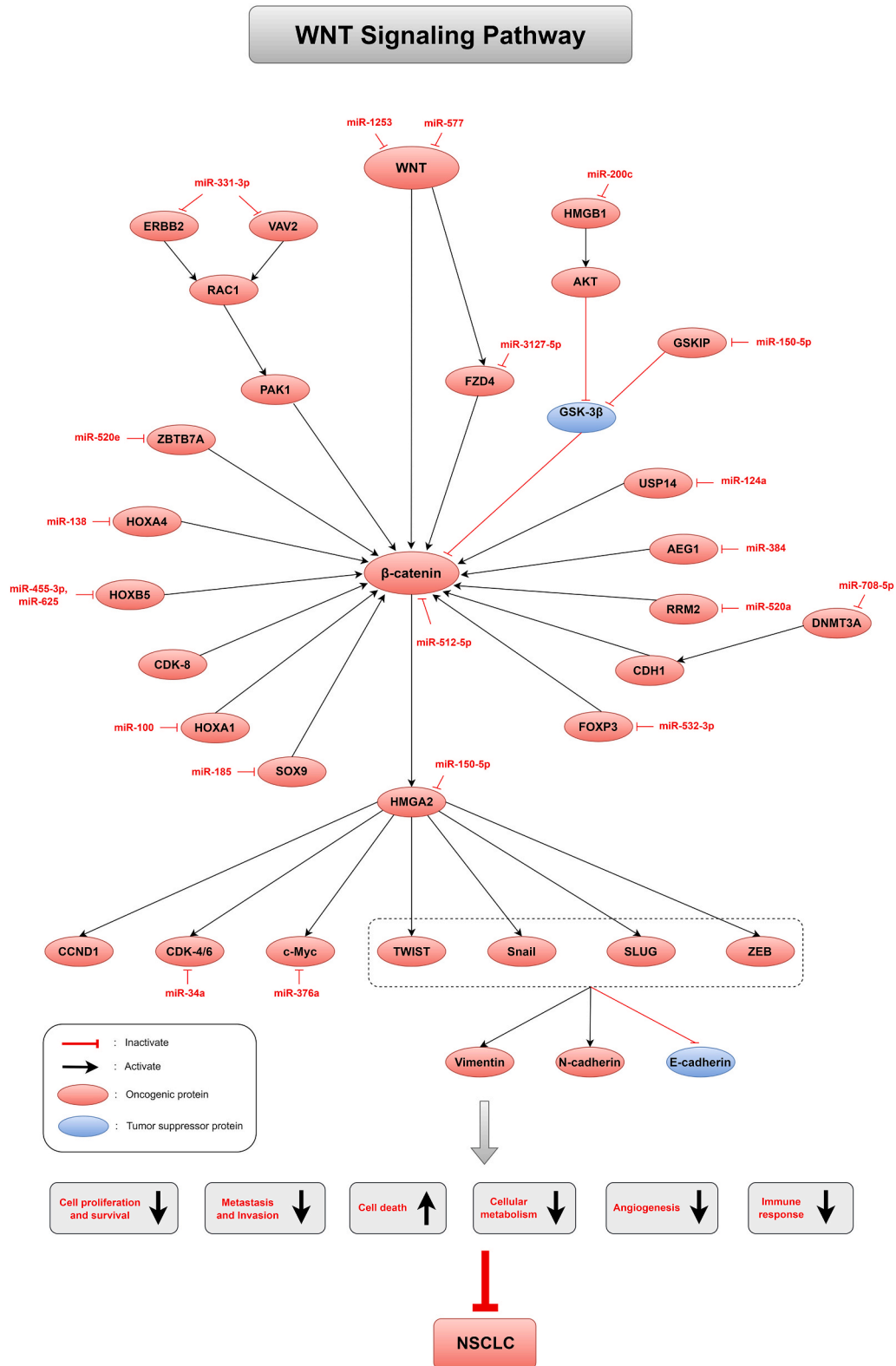
Fig. 3. The potential of miRNA in deactivating the WNT signaling pathway for treating NSCLC. Legend: These miRNAs inhibit the activation of the WNT signaling pathway in NSCLC, which results in the inhibition of cell proliferation, metastasis, invasion, and the promotion of apoptosis, both *in vitro* and *in vivo* [117,156,157,159–173].

2.1. Association of miRNAs with oncogenic signaling pathways

2.1.1. PI3K signaling pathway

The PI3K pathway is one of the most significant intracellular pathways that govern multiple cancer-related events, such as tumor proliferation, growth, and survival [11]. Key proteins of this pathway include phosphatase and tensin homolog (PTEN), PI3K, Ak strain transforming (AKT), and mammalian target of rapamycin (mTOR) [11]. Dysregulation of this pathway commonly arises from mutations in susceptible genes of the kinases, reduced expression and activity of tumor suppressor gene PTEN, amplification of PI3K, and the activation of tyrosine kinase growth factor receptors or upstream oncogenes that interact with PI3K [10,74–76]. This oncogenic dysregulation of PI3K pathway leads to the development of various human cancer types by initiating abnormal processes like cell proliferation, metastasis, angiogenesis, epithelial-to-mesenchymal transition (EMT), chemoresistance, and apoptosis [11,12].

Recently, researchers have investigated the roles of miRNAs in regulating PI3K pathway-related NSCLC progression. For instance, Song et al. (2016) used miRNA-126 to target PI3K in order to increase PTEN expression; and subsequently reduced AKT phosphorylation [77]. This approach successfully suppressed A549 cell proliferation, metastasis, and invasion [77]. Another *in vivo* study has also shown that miRNA-126-encapsulated exosomes could inhibit NSCLC growth and metastasis, leading to a reduced number of metastatic lung nodes in nude mouse models [78]. Additionally, the overexpression of miRNA-133b and miRNA-145 diminished epidermal growth factor receptor (EGFR) expression; hence reducing PI3K, AKT, and cyclin D1 (CCND1) levels while inducing Bax protein expression in A549 cells [79,80]. Thereby, miRNA-133b and miRNA-145 could inhibit this cell line from proliferating while inducing apoptosis [79,80]. Another critical protein of this pathway is mTOR, which plays an essential role in cell proliferation, metastasis, and especially radio sensitivity [81,82]. mTOR expression was reported to be inhibited by miRNA-99a and miRNA-101-3p, resulting in the increase of radio sensitivity of A549 cells both *in vitro* and *in vivo* [82,83]. These preliminary pieces of evidence suggest that miRNAs (Fig. 1) could control NSCLC development through influencing the expression of various genes in PI3K signaling pathway.

2.1.2. RTK/RAS/MAPK signaling pathway

The RTK/RAS/MAPK signaling pathway is another primary oncogenic pathway that highly altered in lung cancer patients [122]. This pathway regulates cell proliferation by receiving extracellular signals through receptor tyrosine kinases (RTKs) and subsequently activating its sub-pathways, such as the Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and rat sarcoma virus/rapidly accelerated fibrosarcoma (RAS/-RAF), via a cascade of intracellular signal (Fig. 2) [14,123–126]. Together, these sub-pathways govern processes like cellular proliferation, migration, and apoptosis [13,14].

The JAK/STAT pathway includes three major components: RTK, JAK, and STAT, with STAT3 (a member of STAT family) acting as a transcription factor that activates cell cycle-regulated genes in the nucleus [124,145]. In lung cancer, STAT3 is constitutively activated, which promotes survival and treatment resistance [146]. Based on these findings, miRNA-202 and miRNA-454 were used to target STAT3 mRNA's 3′UTR region, preventing its translation and then successful inhibiting proliferation, migration, and invasion in A549 and H1299 cell lines [127,128]. Similarly, Sun et al. (2016) have demonstrated that miRNA-9600 augmented paclitaxel and cisplatin sensitivity by downregulating STAT3 and promoting chemotherapy-induced apoptosis in nude mice models [147]. Another study reported that the MAPK/ERK pathway impacts carcinogenesis and treatment resistance of NSCLC cells by driving proliferation and inhibiting apoptosis; thus, targeting members of this pathway is considered a potential therapy for NSCLC [148]. In detail, silencing mitogen-activated protein kinase kinase kinase 9 (MAP3K9) by miRNA-148a–3p significantly suppressed tumor development, cytoskeleton remodeling, and EMT process in A549 and NCI-H1299 cells [129]. In addition, the RAS/RAF sub-pathway, is frequently activated abnormally in several cancers, including NSCLC [149]. Researchers have found that using miR-135 not only effectively inhibited RAB1B protein expression but also led to reduced levels of its interacting protein RAS and other components of the RAS/RAF pathway [150–152]. As a result, the proliferation, invasion, and metastasis of NSCLC cells were strongly suppressed [152]. These results indicate that certain miRNAs (Fig. 2) could improve the outcome of NSCLC cancer treatment by silencing oncogenes in RTK/RAS/MAPK pathway.

2.1.3. WNT signaling pathway

The WNT signaling pathway consists of the WNT/β-catenin dependent sub-pathway and the non-canonical β-catenin independent sub-pathway. It plays a crucial role in transmitting extracellular signals to regulate various intracellular processes, including cell motility, cell polarity, cell proliferation, and differentiation [17–20]. Recent studies have also highlighted the significant impact of this pathway on NSCLC oncogenesis, drug resistance [21], and stem cell self-renewability [153–155]. Therefore, targeting key components of this pathway (e.g., WNT and β-catenin) is a critical strategy in NSCLC control both *in vitro* and *in vivo* [21]. Notably, Liu et al. (2018) and Wang et al. (2018) identified miRNA-1253 and miRNA-577 as tumor suppressors that directly downregulate WNT5A and WNT2A respectively, subsequently inhibiting lung cancer cell's proliferation, migration, and EMT process [156,157]. There are two strategies to inhibit β-catenin expression using miRNAs: direct targeting β-catenin or indirect targeting its upstream genes. For examples, miRNA-512-5p mimics was introduced into A549 cells to target β-catenin [158], while miR-100 and miR-625 was employed to target HOX transcription factors (upstream genes of B-catenin), in NSCLC treatment [159,160]. Both strategies led to reduced β-catenin levels and subsequently affected the expression of its downstream genes, including CCND1, matrix metalloproteinases (MMP), c-Myc and notably, EMT-related genes such as E-cadherin, N-cadherin and Vimentin (Fig. 3) [158–160]. As a result, these miRNAs could significantly inhibit NSCLC cell proliferation, metastasis, invasion, and promote apoptosis, both *in vitro* and *in vivo* [158–160]. In summary, using tumor suppressor miRNAs (Fig. 3) to target and disrupt the activation of the WNT signaling pathway offers a promising tool for NSCLC treatment.

2.2. Participation of miRNAs in anti-tumorigenic RB signaling pathways

The RB pathway plays a central role in regulating cell cycle progression and cell death by either activating or inhibiting its components, including RB, cyclin (CCD), cyclin-dependent kinase (CDK), and E2F-family transcription factors [22]. When CCN associates with its specific CDK, this complex then phosphorylates and inactivates RB proteins, leading to the expression of E2F1/3 for G1/S transition [174]. There are three primary mechanisms through which the RB pathway is inactivated in cancers that exhibit deregulated E2F1/3 activity: (1) loss of RB protein function, (2) overexpression of CDK, and (3) loss of CDK inhibitors [175]. Thus,
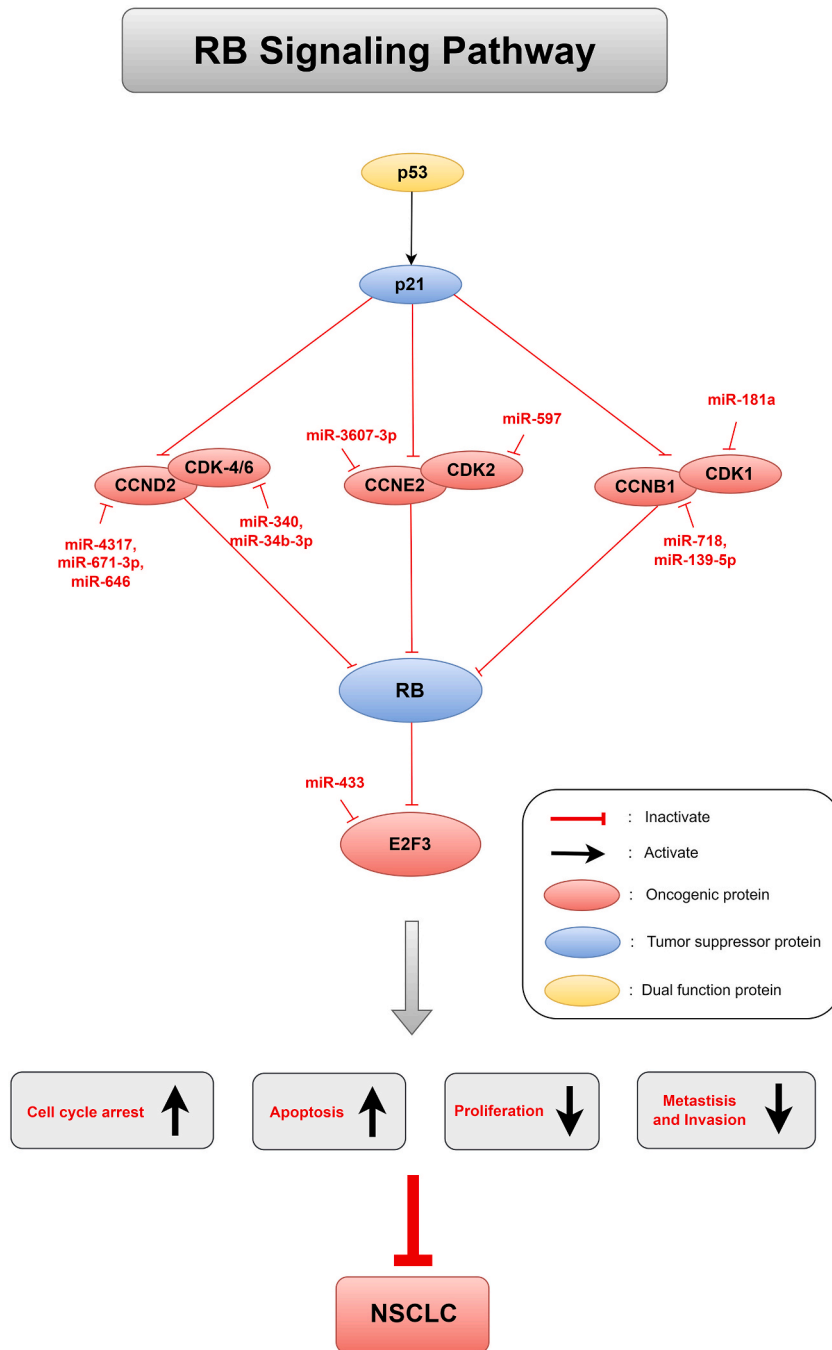

Fig. 4. MiRNAs targeting oncogenes in RB signaling pathway to combat NSCLC progression. Legend: The RB pathway serves as a basic anti-tumorigenic pathway. Thus, introducing these anti-tumor miRNAs targeting the RB pathway could significantly reduce NSCLC malignancy [87, 176–178,180–186].

inhibiting the overexpression of these oncogenic proteins (CCN, CDK, and E2F1/3) in tumor cells could be considered a novel therapeutic approach for NSCLC [22].

Researchers have shown that CCND2 mRNA was a direct target of miRNA-671-3p and miRNA-646; hence, the overexpression of these miRNAs significantly suppressed CCND2 levels, then inhibiting proliferation and invasion of NSCLC cells [87,176]. Additionally, low levels of miRNA-34b-3p and miRNA-340 were detected in NSCLC and were found to be positively correlated with metastasis and tumor size. Therefore, introducing these miRNAs into cancer cells proved effective in suppressing proliferation, inducing cell cycle arrest, and promoting apoptosis in NSCLC cell [177,178]. Overexpression of E2F transcription factor 3 (E2F3) is also frequently found in several cancer types, including NSCLC [179]. Thus, Liu et al. (2018) used miRNA-433 to downregulate E2F3 expression, significantly reducing the proliferation and invasion of both A549 and H460 cells [180]. These results suggest the potential of specific miRNAs (Fig. 4) in targeting RB signaling pathway components to suppress cell proliferation, migration, and invasion while promoting
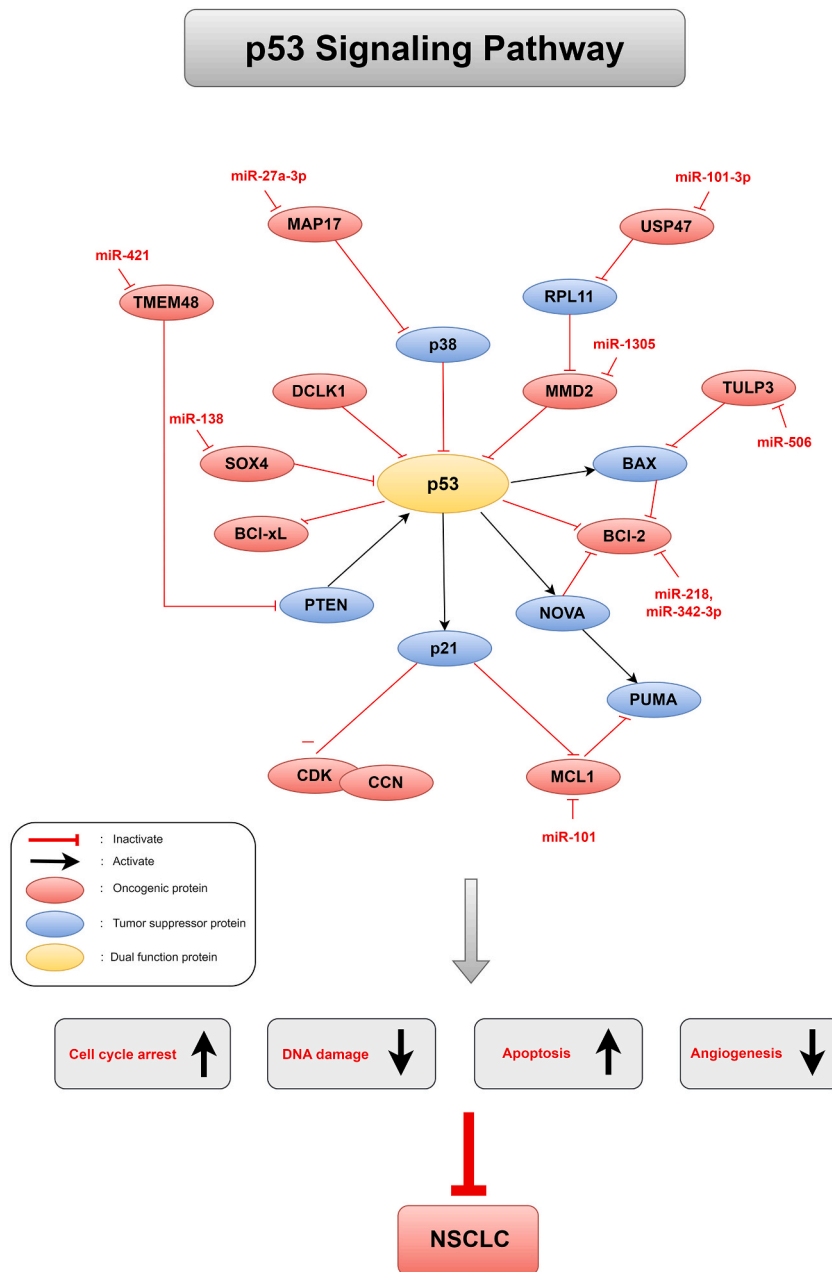

Fig. 5. MiRNAs participating in the p53 signaling pathway contribute to the suppression of NSCLC development. Legend: Alterations in p53 levels can have a significant impact on cell proliferation, including the initiation of NSCLC tumors. capability to restore the normal p53 pathway, resulting in the inhibition of NSCLC proliferation, growth, metastasis, and promotion of apoptosis [191,192,196–202].

apoptosis in NSCLC.

2.3. MiRNAs are involved in the signaling pathways with dual effects on tumorigenesis

2.3.1. p53 signaling pathway

P53 pathway plays crucial roles in regulating cellular responses to stress signals, like DNA damage repair, cell cycle arrest, aberrant proliferation, and apoptosis promotion [24]. The key factor, p53, protects the DNA integrity by undergoing various post-translational modifications and activating the transcription of specific genes involved in cell responses to various stress types [187,188]. Under normal physiological state, p53 is tightly regulated through polyubiquitination mediated by murine double minute 2 (MDM2) [24]. When cells are exposed to stress, inhibition of p53 by MDM2 is blocked, allowing p53 to govern a wide range of cellular responses via the transactivation of its downstream genes [24]. However, this strict regulation is disrupted in cancer cells due to mutations in both *TP53* and its regulator [189,190]. Besides the loss of function mutation, which extremely widespread in human cancers, scientists

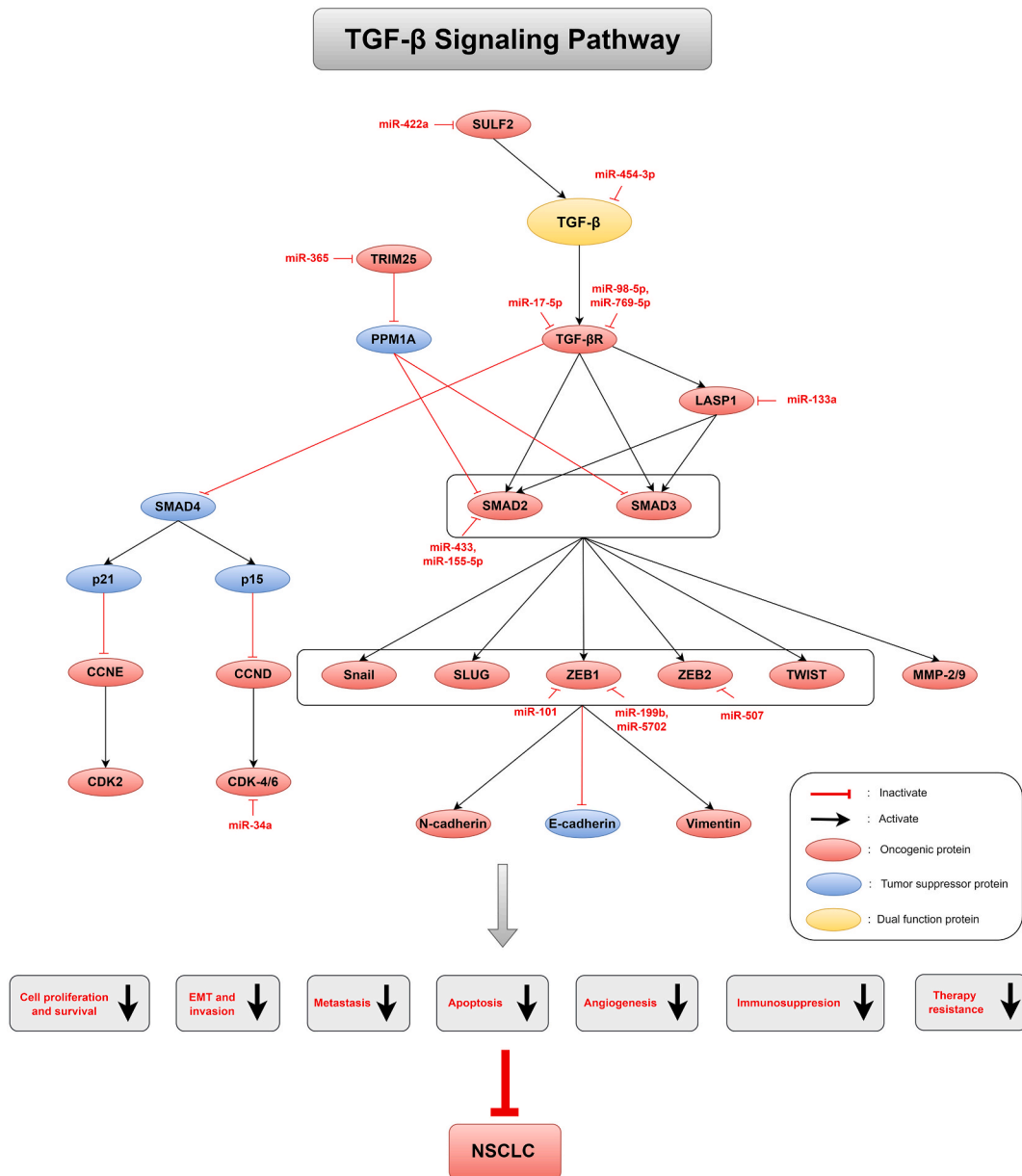**Fig. 6.** MiRNAs employed to rescue the normal state of dual-effected TGF-β signaling pathway in NSCLC tissues. Legend: Abnormal TGF-B over-expression can either inhibit or promote tumors, depending on the stage of cancer cells. Using these miRNAs to inhibit specific genes in this pathway may help suppress proliferation, metastasis, and invasion while promoting apoptosis in NSCLC cells [209,211,214–224].

recently discovered that *TP53* also has a gain of function mutation that makes it accumulate to very high levels in cancer cells and drives lung oncogenesis [23]. Therefore, maintaining a normal level of p53 protein is essential for cancer treatment.

Supporting this idea, Cai et al. (2019) found that the translation of MDM2 was associated with low concentration of miRNA-1305 in NSCLC cells; hence, overexpressed miRNA-1305 substantially decreased proliferation and migration while promoting apoptosis of
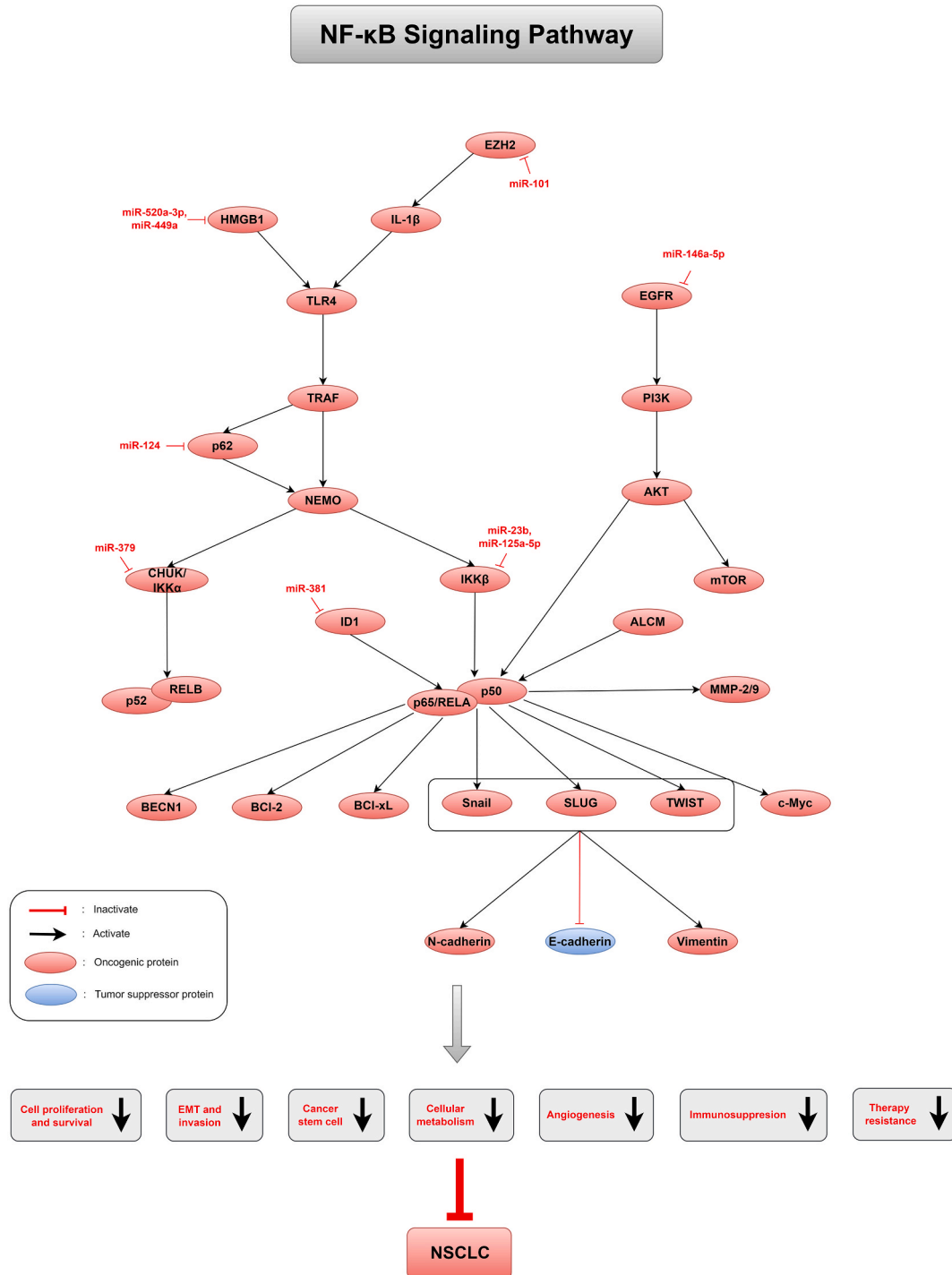
Fig. 7. MiRNAs involved in regulating the NF-κB signaling pathway to restore the normal state of NSCLC. Legend: The NF-κB signaling pathway regulates various cellular processes, and abnormalities in this pathway can contribute to cancer development. Utilizing these miRNAs to target and silence oncogenes within this pathway has shown promise in inhibiting cell proliferation, metastasis, invasion, and migration, while also inducing apoptosis of NSCLC [231,233–239].

A549 and H460 cells [191]. Additionally, ribosomal protein L11 (RPL11) could prevent MDM2-mediated p53 degradation by interacting with MMD2 [192]. However, RPL11 activity is negatively controlled by ubiquitin-specific peptidase 47 (USP47) protein [193]. In this context, silencing USP47 mRNA by miRNA-101-3p could increase RPL11 level and then helped to reduce cancer cells by stabilizing p53 [192]. Overexpression of cyclin B1 (CCNB1), which initiates mitosis, is common in NSCLC cells and correlates with tumor differentiation and vascular invasion [194]. Hence, downregulating CCNB1, achieved by miRNAs like miRNA-718 or miRNA-139-5p, significantly suppressed NSCLC cell proliferation, migration, invasion, and promoted apoptosis [184,185]. Given the importance of cell apoptosis regulation in cancer therapy, miRNA-based strategies to restore the normal p53 pathway (Fig. 5) have been vigorously pursued in recent years and pave the way for pre-clinical trials in cancer treatment [195].

2.3.2. TGF-β signaling pathway

The transforming growth factor-β (TGF-β) signaling pathway is critically involved in a wide range of cellular processes, including cell differentiation, cell proliferation, and cell-specific and tissue-specific motility [26–28]. In this pathway, TGF-β mediates numerous embryonic and adult signaling functions by binding to its receptor kinases to initiate downstream signaling of SMAD proteins, ubiquitin ligases, and/or intracellular protein kinases. These signals then govern gene-specific expression, RNA processing, and mRNA translation, resulting in the regulation of specific protein expression [28,203–205]. Depending on the stages, the TGF-β signaling pathway also has dual effects on cancer development [206]. In early stages, TGF-β functions as a tumor suppressor by inhibiting cell growth and inducing apoptosis, whereas in advanced stages, TGF-β becomes a powerful pro-metastasis factor that promotes the EMT process [206–208]. Therefore, the use of miRNAs to target and silence TGF-β proteins or their receptors holds promise for restricting the proliferation, metastasis, and invasion of advanced NSCLC.

This was demonstrated in NSCLCL cells and tissues through the work Liao et al. (2021), who used miRNA-454-3p to counter the overexpression of TGF-β2, and in studies by Li et al. (2017) and Yang et al. (2017), who employed miR-17-5p and miR-769-5p respectively to lower the expression of TGF-β receptors [209–211]. Not only TGF-β but also SMAD modifications, such as TGF-β-mediated SMAD activation or epigenetic modifications via miRNAs, contribute to NSCLC progression [212,213]. Based on the correlations between low levels of miR-433 and the overexpression of SMAD in NSCLC, Li et al. (2015) overexpressed this miRNA in NSCLC for therapeutic purposes [214]. This intervention downregulated SMAD2 protein as well as decreased the levels of CCND1, matrix metalloproteinases-2/tissue inhibitor of metalloproteinases-2 (MMP-2/TIMP-2), and MMP-9, which led to suppressing NSCLC proliferation, metastasis, and invasion [214]. Based on these data, several miRNAs (Fig. 6) could be used to rescue aberrant TGF-β signaling pathways in cancer progression and pull them back to the normal control state.

2.3.3. NF-κB signaling pathway

NF-κB signaling pathway is one of the hot spots in cancer research, involved in inflammatory or immune responses, as well as regulation of cell differentiation, proliferation, metastasis, and apoptosis [225,226]. Similar to the p53 and TGF-β signaling pathways, the NF-κB pathway exhibits dual roles in tumorigenesis [31]. However, its role in promoting cancer is generally more common and well-evidenced than the anti-tumorigenesis role. NF-κB has influence on tumor development and progression by excessive innate immunity activation, abnormal cell growth, and dysregulation of EMT-related transcription factors [227–229]. Mutations in upstream NF-κB effectors also activate NF-κB, and then specifically target the promoters of other oncogenes which leads to tumor malignancy [230]. Based on this knowledge, scientists sought to discover miRNAs (Fig. 7) that could reduce the expression of genes involved in the NF-κB pathway activation. For example, in a study by Huang et al. (2018), they have demonstrated that inhibitor of DNA binding 1 (ID1) overexpression led to the NF-κB pathway activation and using miRNA-381 to knockdown ID1 successfully inhibited NSCLC proliferation and growth, while promoting cisplatin sensitivity [231]. Besides, Jiang et al. (2020) found that silencing activated leukocyte cell adhesion molecule (ALCAM), which is a member of the immunoglobulin superfamily, by miRNA-148 could suppress EMT through deregulating N-cadherin and vimentin, ultimately blocking the metastasis and invasion of NSCLC cells [232], https://onlinelibrary.wiley.com/doi/10.1111/1759-7714.13285. Similar outcomes were observed in studies where miRNA-449 and miRNA-379 targeted high mobility group box 1 (HMGB1) and conserved helix-loop-helix ubiquitous kinase (CHUK), respectively [233, 234]. Besides aforementioned functions, several recent studies have suggest that NF-κB also operates as a tumor suppressor by activating the transcription of the Fas ligand [31]. However, there is a limited amount of research on the role of miRNAs in regulating this function of NF-κB.

2.4. Limitations of miRNAs in therapeutic uses

In NSCLC, miRNAs have shown important roles in mediating and regulating a variety of cancer-related pathways, which implicate their role in carcinogenesis, more importantly, the cancer therapeutic treatments [240–242]. However, utilizing miRNAs for clinical purposes has also faced lots of bottlenecks and limitations, including the intrinsic characteristics of miRNA, such as less stability and challenge to reproduce in miRNA preparations [243–245]. Other common barriers to miRNAs in clinical use are the complexity of identifying miRNA targets and discerning miRNA biological functions which results in mal-functional miRNAs or off-target effects [245,246]. Delivering miRNAs to specific targets is also challenging due to their journey through the circulatory system, potential immune cell phagocytosis, and endonuclease degradation, as well kidney filtration [246,247]. Furthermore, miRNA use can lead to adverse reactions, such as miRNA-mediated toxicity which disrupt specific gene expression and slowdown drug and toxicant metabolism [245,248]. For example, overexpression of miR-24 and miR-34a has been reported to inhibit the expression of hepatocyte nuclear factor 4 alpha, leading to decreased bile acid production via the cholesterol 7 alpha-hydroxylase pathway [249].

In addition, miRNA may activate the innate immune response, causing a series of non-specific reactions, such as changes in length,

structure, chemical modification of cellular signals, and cytokines production. Recent studies have shown that immunological activities triggered by miRNA reagents might be associated with the transcription of miRNA genes in epithelial cells, which involve the mediation of pathogen recognition receptors, such as Toll-like receptors [250,251]. Another primary concern is the dosage of therapeutic miRNAs for treatment purposes, as an overdose of miRNAs may increase off-target side effects, non-specific immune responses, and toxicity [61,246]. For example, the MRX34 clinical trial was closed because of immune-related toxicity, mainly associated with the properties of miR-34a mimics and the dosage used [252]. To enhance stability and biological activity, most commercial miRNA-based drugs undergo various chemical modifications or length adjustments. Therefore, it is essential to thoroughly evaluate different miRNA-derived drugs in terms of characteristics and dosages to achieve better efficacy and maximum biosafety for specific therapeutic applications.

3. Delivery tools for miRNA therapeutic approaches

MiRNAs are naked nucleic acids; hence, they can easily get degraded by nucleases or absorbed by macrophages, as well as trapped by the host immune system. In addition, the delivery of miRNAs to the targeted cells could pose another difficulty in developing miRNA-based therapy for cancer treatment. As a result, it is crucial to develop stable and effective vectors that can protect these cargoes and efficiently deliver them to the target cells. Several systems could fulfill the need for vector development (Fig. 8).

3.1. Virus-based vector system

One of those, a virus-based vector system, is a traditional tool for miRNA delivery, typically including retroviruses, lentiviruses, adenoviruses, or adeno-associated viruses (AVVs) [253,254]. Once the miRNA is cloned into the viral vector, the purified viral particles can be introduced into the target cells through various methods, such as tissue-direct injection or intravenous administration, to release the miRNAs [255,256]. Depending on the viral vector's system used, the miRNA sequence may either integrate into the host cell's genome (retroviruses and lentiviruses systems) [257,258] or exist as an episomal element (adenoviruses system) [51], allowing
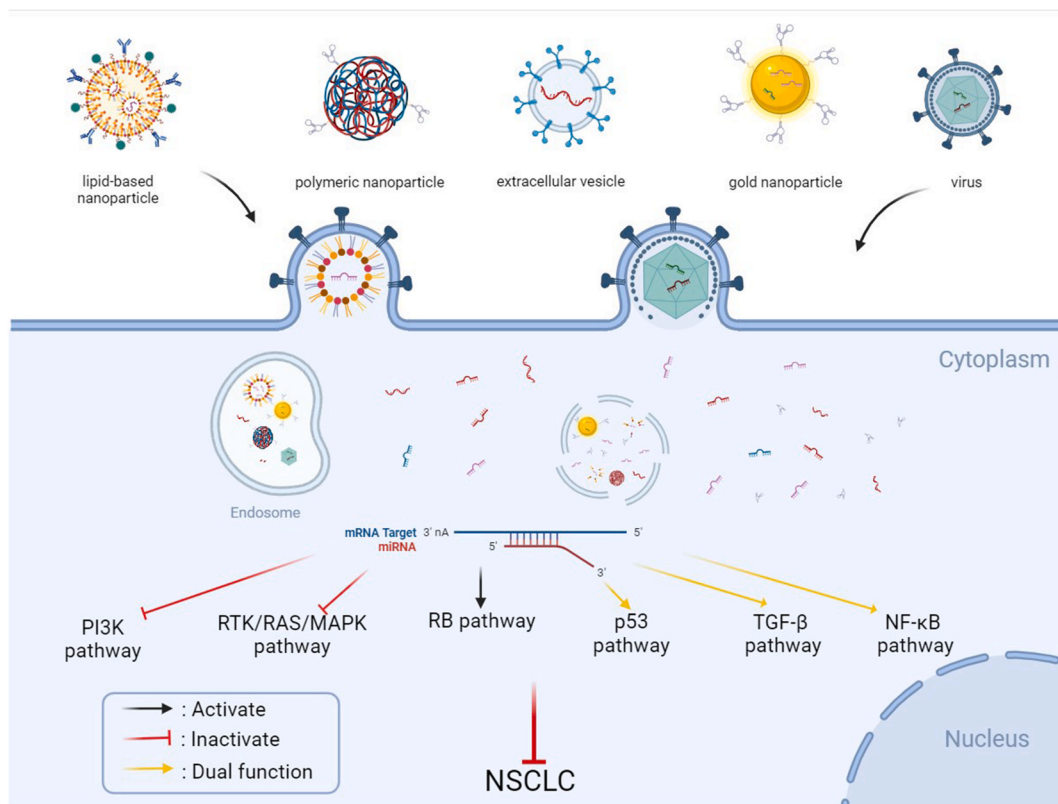

Fig. 8. Mechanism of delivering therapeutic miRNAs by current delivery tools into NSCLC cells to target cancer-related pathways. Legend: The most popular tools for delivering therapeutic miRNA to target cells include viral vectors and non-viral systems, such as polymer-based, lipid-based, EV-based delivery systems, and inorganic nanoparticles. These carriers can either form complexes with miRNA or encapsulate it for efficient transport to target cells via receptor-mediated endocytosis. Once released into the cytoplasm, these miRNAs interact with their target mRNAs to deactivate oncogenic proteins involved in seven common pathways, including PI3K, RTK/RAS/MAPK, WNT, RB, p53, TGF-β, and NF-κB pathways. Consequently, NSCLC proliferation, metastasis, metabolism, and treatment resistance are inhibited, while apoptosis is enhanced.

stable and long-lasting expression of miRNAs to regulate cancer cells' gene expression [254]. Several studies have shown that some miRNAs were significantly increased in virus-infected cells; for example, miRNA-138 has upregulated 1000 folds in retroviral-infected mouse embryonic fibroblasts to enhance induced pluripotent stem cell reprogramming [198]. Among these viral vectors, oncolytic adenovirus is commonly used in cancer treatment owing to its commendably tumor-restricted replication abilities [259]. Thanks to this finding, Chang et al. (2013) successfully generated an oncolytic adenoviral vector named AdCN205, which overexpressed miR-34a and presented strong anti-tumorigenesis results [260]. Despite the high transfection and infection efficiency, viral vectors are limited in wide application due to their toxicity, immune system stimulation, and tissue degeneration [261].

3.2. Non-viral delivery systems

To avoid virus-based delivery's limitations, nanoparticles (NPs), including gold nanoparticles (AuNPs), iron oxide nanoparticles, or organic nanoparticles such as liposomes, are widely used due to their straightforward synthesis and functionalization properties, especially low immunogenicity and cytotoxicity [262–264].

3.2.1. Polymeric nanocarriers

Polymeric nanocarriers, which have been widely studied for miRNA delivery, include three main systems of polyplexes, poly lactic-*co*-glycolic acid (PLGA), and dendrimers [265,266]. MiRNAs can be loaded into these delivery systems by complexation through electrostatic interaction, direct conjugation by covalent linkers, or encapsulation during the nanoparticle formulation process [265, 267]. These nanocarriers share a common mechanism for miRNA delivery, initiated by forming complexes between positive-charged polymers and miRNAs. These complexes can interact with either negative-charged cell membranes or specific proteins, thereby facilitating their cellular uptake through endocytosis [268]. Inside the cells, these complexes absorb protons from endosomes, leading to the disruption of endosomes and the release of them into the cytoplasm [269]. Once these complexes disassemble, miRNAs are liberated and then bind to target mRNAs to regulate gene expression in cancer-related cellular processes.

Polyethyleneimine (PEI), the most common type of polyplexes, was used to deliver miR-33a and miR-145 to colon carcinoma tissues in a mouse model, resulting in tumor proliferation reduction and cell apoptosis increase [270]. Another study used a three-layered polyplex of a PEI core, a polyethylene glycol (PEG) intermediate layer, and a folic acid-modified chitosan outer layer to systemically deliver miRNA-126 into lung cancer cells [271]. The results showed that this polyplex could efficiently deliver miRNA-126 and inhibit tumor growth *in vivo* [271]. PLGA NPs could increase their miRNA encapsulation efficiency by preparing with positively charged molecules like PEI or chitosan [272,273]. Arora et al. (2014) revealed that PLGA NPs loaded with miR-150 mimics and prepared with PEI could successfully deliver and release miR-150 mimics to pancreatic cancer cells to reduce cell migration and invasion [272]. By coated with the chondroitin sulfate, poly(amidoamine), the most common type of dendrimers, improved its targeting ability and successfully delivered miR-34a to pancreatic cancer cells [274]. As a consequence, cell proliferation and migration were significantly inhibited by the activation of apoptosis and cell cycle arrest [274]. These results support further investigation in the use of polymer-based miRNA delivery systems. However, despite their ability to achieve efficient transfection and tumor specificity [275], their application in clinical is still limited by their high toxicity [265]. This could be because the positive charge of polymers could enhance cellular uptake, but it also destabilizes negatively charged cell membranes [276]. One solution to ease this toxicity is to shield the positive charges through acetylation [277], hydroxylation [278], or modify their surfaces with PEG moieties [279].

3.2.2. Inorganic nanoparticles

Gold nanoparticles are often functionalized with thiol or amine groups on their surfaces, enabling them to effectively bind to miRNAs and load them onto the NPs [66]. Additionally, ligands or antibodies specific to receptors on the surface of target cells can be attached to the AuNPs' surface to increase their stability and targeting ability [280]. Subsequently, the AuNPs can be up taken through endocytosis and intracellular delivery [281] and then release the miRNA cargo due to changes in pH or cellular processes that break down the surface linkages of the NPs [269]. Ultimately, the delivered miRNAs can exert their regulatory function inside the target cells, effectively modulating gene expression required for cancer treatment. However, these nanoparticles have significant limitations, such as low encapsulation efficiency, poor stability, and slow endosomal escape [281]. To overcome these obstacles, lipid nanocomplexes have been conjugated with a functional group known as PEG [254]. In one study, Ghosh et al. (2013) tested 35 formulations of miRNA-AuNP-S-PEG and identified miRNA-1-AuNP10-S-PEG0.5 as the optimal polyelectrolyte complex due to its greater transduction efficiency, lower toxicity, and higher ability to be taken up by cells through endocytosis [281]. Besides gold nanoparticles, iron oxide nanoparticles have recently been applied as novel miRNAs nanocarriers for cancer therapy [282,283]. Arrizabalaga et al. (2022) have attached miRNA-148b to the surface of magnetic nanoparticles by a Diels-Alder cycloadduct [284]. These nanoparticles were then excited by alternating magnetic field radiofrequency to drive the hysteretic heating [284]. As a result of the altered cell membrane properties and the destruction of Diels-Alder bonds, miR-148b mimic was released into A549 cells [284]. Thanks to these achievements, inorganic nanoparticles are becoming one of the most used types of nanomaterials, namely as miRNAs carriers for cancer cells [262].

3.2.3. Organic nanoparticles

Lipid-based nanoparticles were first prepared in 1961, consisting of three major types of charge-based liposomes: cationic, anionic, or neutral. These nanoparticles can either encapsulate miRNAs within their lipid bilayers [285] or form complexes with cationic polyplexes through electrostatic interactions to transport miRNAs to recipient cells [66,261]. In some cases, the surface of lipid-based nanocarriers can be modified with polymers, ligands, surfactants, and fatty acids [286] to control the component release, enhance

Table 2

Advantages and disadvantages of systems used for miRNA delivery in NSCLC.

Delivery system	Advantages	Disadvantages	Solutions	References
Viral vectors	Long-term gene expression; high delivery efficiency	Low loading capacity, high toxicity, strong immunogenicity	Use of oncolytic adenovirus with tumor-restricted replication abilities	[259,301,302]
Non-viral delivery systems				
Polymer nanoparticles	Non-immunogenic response, high encapsulation capacity	High toxicity *in vivo*	Acetylation, hydroxylation, or modification their surfaces with PEG	[277–279]
Gold nanoparticle	Straightforward functionalization, low cytotoxicity	Low encapsulation efficiency, slow endosomal escape; lack of information about uptake, biocompatibility, and cytotoxicity	Conjugation with a polyethylene glycol (PEG) group	[254,262,281]
Iron oxide nanoparticle	Low toxicity, biodegradability, low cost, ease of surface modification	Information about *in vivo* distribution, uptake ability, and biocompatibility have not been clarified	Functionalization with polyethyleneimine group	[262,303,304]
Lipid-based nanoparticle	Non-pathogenic and non-immunogenic response; low toxicity, biodegradable	Short half-lives in sera; low delivery efficiency; moderate loading capacity	Conjugation of the lipids with hydrophilic and flexible polyethylene glycol (PEG) group	[254,261,305,306]
Extracellular vesicles	Low cytotoxicity and negligible antigenicity; inner cargos protection, specific targeting	Low uptake rate and rapid clearance mediated by the mononuclear phagocytic system; low transfection efficiency	Fusion with the "don't eat me" CD47 signal and the "eat me" homing signal in membrane; use of commercial kit Exo-Fect	[254,292,296,299,300]

penetration efficiency, and target medication delivery [287]. Similar to inorganic nanoparticles, target cells take up these nanoparticles, and endosomes' pH changes then prompt miRNA release into the cytoplasm, enabling their functional activities [269]. Wu et al. (2013) have shown that the delivery of miR-29b by the cationic lipoplex system increased miR-29b expression in NSCLC tumors by approximately 5-fold and significantly inhibited tumor growth by nearly 60% [288]. Additionally, CD59 receptor-targeted delivery of miRNA-1284 and cisplatin-loaded liposomes has been shown to have an enhanced therapeutic effect against cervical cancer cells [289].

These results indicated that nanocarriers are remarkably effective in miRNA delivery to target cells, which leads to improvement in cancer treatment; however, studies elucidating the artificial nanoparticles' safety have not been clarified [290,291]. Generally, viral and non-viral miRNA delivery systems have both advantages and disadvantages [261]. Despite higher transfection efficiency, the viral vector is more toxic and can trigger immunological responses [261]. In contrast, non-viral vectors are safer but have low delivery efficiency [261]. Thus, there is an urgent need to find a novel, more effective, and safe tool in miRNA delivery that could overcome both conventional systems' limitations.

3.2.4. Biological nanoparticles

Biological vesicles have emerged as potential candidates for this purpose. Scientists recently discovered a remarkable function in delivering bioactive materials from donor to recipient cells of nano-sized particles naturally secreted by cells, which are extracellular vesicles (EVs) [292]. Since they are biocompatible with cells, they have been marked as one of the most promising nanoparticles for use in specialized cancer treatment.

Besides the natural presence of miRNA contents in EVs, several strategies have been applied to load and enrich selective miRNAs into EVs, which are incubation, electroporation, and sonication [293,294]. Theoretically, incubation desired miRNAs with EVs under $CaCl_2$-supplemented conditions could promote the interaction between them, enhancing the encapsulation of miRNA into EVs [293, 294]. Unfortunately, using this separately did not successfully load miRNAs into EVs [295]. Indeed, Zhang et al. (2017) have applied additional heat shock to the EVs membrane, that result, formed the miRNA-$CaCl_2$ complex, which could be introduced into EVs [293]. Another standard method, electroporation, uses an electrical pulse to create nanometer-scale pores in the membrane, allowing the loading of miRNAs into EVs [295]. However, the leakage of endogenous cargoes through large-size pores, such as miRNA and protein, may impact the therapeutic efficiency of miRNA within EVs [294]. In recent studies, researchers have shown that using sonoporation technology to induce cell membrane permeabilization could increase the absorption of therapeutic agents, including miRNAs [295]. Although these strategies have successfully introduced miRNA into EVs, they still cope with the limitation of low transfection efficiency [293,295]. Therefore, recently launched in the market, the commercial kit Exo-Fect offers a promising technique with greater than 50% transfection efficiency and more than 1000-fold upregulation of the interested miRNA [293,296]. Abreu et al. (2021) pre-treated EVs with Exo-Fect reagent to deliver miRNA-155-5p into cells and found that Exo-Fect could modify EVs membrane properties [296]. As a result, miRNA-155 loaded into EVs easily, and the alteration in the Exo-Fect-loaded EVs membrane enhanced the stability of EVs within the target cells as well as decreased the interaction of those modulated EVs with lysosomes [296].

MiRNA-loaded EVs enter recipient cells through the interaction between ligands on the EV's surface and receptors on the recipient cell's membrane [297]. The targeting specificity of EV-based systems could be enhanced by genetic engineering or by fusing their surfaces with ligands or homing peptides [298]. Inside the cell, the delivered miRNAs are released into the cytoplasm, where they bind to target mRNAs, thereby exerting their regulation effects on an intracellular signaling pathway that can affect cellular behaviors and functions. Although delivery systems through EVs have more advantages than viral vectors and artificial nanoparticles in terms of biosafety and targeting ability, long-term and considerable challenges in this system are the significant uptake rate and rapid clearance mediated by the mononuclear phagocytic system (MPS) [299]. To address this issue, Belhadj et al. (2020) attempted to achieve MPS escape by fusing the "don't eat me" CD47 signal and the "eat me" homing signal in the exosomal membrane [300]. As a result, this combined strategy acquired a substantial percentage of 123.53% of cancer cell distribution compared to traditional nanocarriers [300]. Overall, besides using conventional nanomaterials, exosomes or EVs could be applied as biological carriers for precisely delivering miRNAs to NSCLC and suppressing tumorigenesis. Table 2 summarizes the advantages and disadvantages of miRNA delivery systems and points to methods that could overcome those obstacles.

Over the last five years, more than two hundred research on miRNAs that successfully suppress NSCLC has been published. These miRNAs have various effects on cancer processes, such as inhibiting proliferation, metastasis, triggering apoptosis, as well as enhancing chemoradiotherapy sensitivity. Thanks to these remarkable research achievements, by 2021, 10 miRNA-based drugs have reached clinical trials, including TargomiRs from EnGeneIC as second or third Line Treatment for patients with non-small cell lung cancer (ClinicalTrials.gov, NCT number: 02369198) [307]. Unfortunately, none of them have entered phase III and a half were halted due to immune-related severe side effects and barriers to drug delivery efficiency, off-target phenomenon [307]. A single miRNA can bind to and target several different mRNAs, making them a double-edged sword when used for multifactorial diseases such as cancer. Moreover, regardless of the achievements of nanomaterial-based platforms for miRNA delivery, perfect tumor targeting has not been achieved since partial nanoparticles still accumulate in the liver and spleen after intravenous administration [307]. Additionally, controlling and validating the distribution and fate-related parameters of nanoparticles certainly contributes to the slow rates in clinical translation [307].

4. Conclusions

In conclusion, the association between miRNAs and NSCLC, various miRNA-based approaches, and cell-specific delivery systems have been discussed. These provide an overview of NSCLC-regulated miRNAs and their target genes in the downstream signaling

pathways for the further potential of miRNA-based anti-tumor therapy. MiRNAs have been detected to regulate genes involved in signaling pathways associated with NSCLC, such as PI3K, RTK/RAS, WNT, RB, p53, TGF-β, and NF-κB. Consequences of these are the inhibition of cancer cell proliferation, migration, and invasion in addition to the promotion of cell apoptosis. Furthermore, despite many techniques developed as miRNA carriers, including viral vectors, nanoparticles, and extracellular vesicles, this field requires more investigation to bring miRNA to the target tumors. Although facing many difficulties, we expect that further studies, both *in vivo* and *in vitro*, could make breakthroughs to bring miRNAs and miRNA carriers into clinical NSCLC treatment and bring hope to patients and researchers.

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Data availability statement

All data generated or analysed during this study are included in this published article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AKT	ak strain transforming
ALCAM	activated leukocyte cell adhesion molecule
AVVs	adeno-associated viruses
BCl	B-cell lymphoma
BCl-xL	B-cell lymphoma extra-large
CCNB	cyclin B
CCND	cyclin D
CDK	cyclin-dependent kinase
CHUK	conserved helix-loop-helix ubiquitous kinase
E2F3	E2F transcription factor
EGFR	epidermal growth factor receptor
EMT	epithelial-to-mesenchymal transition
EV	extracellular vesicle
ERK	extracellular signal-regulated kinase
HMG	high mobility group box
HOX	homeobox
ID	inhibitor of DNA binding
JAK	janus kinase
LPs	lipoplexes
MAPK	mitogen-activated protein kinase
MAP3K	mitogen-activated protein kinase kinase kinase
miRNA	microRNA
MDM	murine double minute
MMP	matrix metalloproteinases
mTOR	mammalian target of rapamycin
MPS	mononuclear phagocytic system
NF-κB	nuclear factor-kappa B
NSCLC	non-small cell lung cancer
NP	nanoparticles
PEG	polyethylene glycol
PEI	polyethyleneimine
PLGA	poly lactic-*co*-glycolic acid
PI3K	phosphoinositide 3-kinase
PTEN	phosphatase and tensin homolog

RAB	RAS-associated binding
RAC	RAS-related C3 botulinum toxin substrate
RAF	rapidly accelerated fibrosarcoma
RAS	rat sarcoma virus
RB	retinoblastoma
Rho	rhodopsin
RP	ribosomal protein
RTK	receptor tyrosine kinase
SMAD	suppressor of mothers against decapentaplegic
STAT	signal transducer and activator of transcription
TGF-β	transforming growth factor β
TGF-βR	transforming growth factor β receptor
TIMP	tissue inhibitor of metalloproteinases
USP	ubiquitin specific peptidase
UTR	untranslated region
WNT	wingless/Integrated

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