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Current landscape of miRNAs and TGF-β signaling in lung cancer progression and therapeutic targets

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ABSTRACT

Lung cancer (LC) is the primary reason for cancer-associated fatalities globally. Due to both tumor-suppressing and tumor-promoting activities, the TGF-β family of growth factors is extremely essential to tumorigenesis. A non-coding single-stranded short RNA called microRNA (miRNA), which is made up of about 22 nt and is encoded by endogenous genes, can control normal and pathological pathways in various kinds of cancer, including LC. Recent research demonstrated that the TGF-β signaling directly can affect the synthesis of miRNAs through suppressor of mothers against decapentaplegic (SMAD)-dependent activity or other unidentified pathways, which could generate allostatic feedback as a result of TGF-β signaling stimulation and ultimately affect the destiny of cancer tissues. In this review, we emphasize the critical functions of miRNAs in lung cancer progression and, more critically, how they affect the TGF-β signaling pathway, and explore the role of both the TGF-β signaling pathway and miRNAs as potential therapeutic targets for improving the treatments of LC patients.

1. Introduction

In the world, one of the top causes of cancer-related death is lung cancer (LC), which is distinguished by the involvement of multiple complexes of signaling pathways in its development and metastasis [1]. LC is the largest cause of cancer death in the United States, dying more than 350 people each day than breast, prostate, and pancreatic cancers together and more than twice colorectal cancer [2]. Environmental elements, including radon, lead, and other airborne harmful contaminants, are thought to be the primary contributors to its occurrence [3]. It is also observed that the number of lung cancer cases recorded is rising proportionally as smoking prevalence rises, especially in developing countries (see Tables 1 and 2).

Traditionally, lung cancer has been divided into the histologic subtypes of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) based on pathologic features and treatment results.

Lung cancer is frequently found in people who have already seen significant disease progression. In order to prevent the progression of the disease by focusing on the tumor cells, surgery is no longer an option, leaving only radiotherapy, chemotherapy, or combination therapy. Unfortunately, these treatments have not always been successful, requiring research for further therapeutic strategies to lower the rate of lung cancer death.

Numerous important activities, such as cellular development, differentiation, apoptosis, motility, invasion, extracellular matrix synthesis, angiogenesis, and immunological responses, are regulated by the

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transforming growth factor beta (TGF-β) signaling cascade [4,5]. The TGF-β superfamily includes TGF-β, TGF-β2, TGF-β3, activins, nodal, and bone morphogenetic protein (BMP) molecules [6,7]. A heteromeric complex of type I (TGF-βRI) and type II (TGF-βRII) receptors is activated by ligand binding, and TGF-βRI is recruited to the complex. After being phosphorylated, SMAD2 and SMAD3 are transported into the nucleus, where they interact with SMAD4 [8] (Fig. 1).

The TGF-signaling cascade is dysregulated or altered in tumor cells, and TGF-β no longer regulates proliferation. Tumors may resist the inhibitory effects of TGF-β signaling as a result of mutations or epigenetic alterations acquired during tumor progression [9]. Furthermore, TGF-β signaling dysregulation has been linked to LC progression, metastasis, and treatment response [10].

MicroRNAs (miRNAs), ranging in size from 18 to 25 nucleotides, can attach to miRNA response elements (MREs) on the 3′UTR of their intended target mRNA, causing the mRNA to be degraded or the translation of the mRNA to be inhibited [11]. Recently, miRNAs are becoming a focal point of research since their dysregulation is associated with different human disorders, most notably cancer [12]. Lung cancer progression is invariably linked to aberrant miRNA expression [13].

Numerous miRNAs have been identified as controllers of the TGF-β signaling pathway in LC, such as miR-21 [14], miR-27a [15], miR-128-3p [16], miR-133a [17], miR-9-5p [18], miR-3305p [19], miR-93, miR-29c, and miR-429 [20]. These miRNAs specifically target TGF-β signaling elements, such as TGF- β receptors, *SMADs*, and downstream effectors; and can influence mechanisms either negatively or positively.

Drugs targeting the TGF-β signaling pathway, essentially TGF-β inhibitors [21], TGF-β receptor antagonists, and TGF-β neutralizing antibodies, are currently undergoing clinical trials [22]. Additionally, miRNA-based therapies, including miRNA mimics, the CRISPR/Cas system, and antagomirs, are also being developed for LC treatment [23,24]. These therapies for cancer are targeted at inhibiting oncogenic miRNAs or restoring tumor suppressor miRNAs in LC cells.

Here, we highlight the fingerprints of miRNAs with the TGF-β signaling pathway in LC progression and explore their potential therapeutic targets in LC patients. Generally, TGF-β signaling and miRNAs are essential contributors to LC progression and spreading. Therapeutic targeting of this pathway has recently shown promise in the treatment of cancer.

2. Biogenesis of miRNAs

The synthesis of miRNAs is a complex mechanism that involves multiple steps and several enzymes. RNA polymerase II initiates miRNA gene transcription, which produces primary miRNA (pri-miRNA) transcripts that can be hundreds or thousands of nucleotides in length [25]. Pri-miRNAs have a hairpin structure with a stem loop, which is recognized and cleaved by a complex of proteins called Drosha/DGCR8 within the nucleus to produce precursor miRNA (pre-miRNA) of around 70 nt in length (Fig. 2) [26].

The pre-miRNA is then translocated by exportin-5 and RanGTP into the cytoplasm. Within the cytoplasm, pre-miRNA is further processed by the RNase III enzyme Dicer, along with its cofactor TRBP, to create a miRNA duplex [27]. The miRNA duplex is composed of the mature miRNA and its complementary miRNA strand [28].

The complementary base pairing between the mRNA and the miRNA subsequently directs the miRNA to the target mRNA. This process is carried out by the RNA-induced silencing complex (RISC) [26]. The RISC complex can then either inhibit translation or degrade the target mRNA, leading to a reduction in the activity of the target gene [29].

The biogenesis of miRNAs is tightly regulated and can be modulated by various factors, including transcription factors [30], epigenetic modifications [30], and RNA-binding proteins [31]. Many disorders, including cancer, have been linked to inadequate regulation of miRNA biogenesis. However, the synthesis of miRNAs is a multi-enzyme and multi-step process that is highly regulated. Knowing the molecular pathways of miRNA biogenesis is critical for the development of

Table 1
Roles of oncogenic miRNAs in TGF-β signaling pathway with their targeted genes and effects.

MiRNA	Human models	Animal models	Cell Line study	Mechanism of Action	Effect	Ref.
miR-3614-5p	179 paired sample	Nude mice	A549, 16HBE, H1299, SK-MES-1, NCI–H226	↑ TGF-β ↑ PGAM1	↑ Progression	[63]
miR-128-3p	–	Mice	H292, HLAMP, Calu-3, SK-MES-1, luc-M38, H520, H1299, H596, H1650, H1975, PAa, 95D, LL/2- BEAS-2B, A549	↑ TGF-β ↑ Wnt/β canetin	↑ Metastasis ↑ cell renewal	[69]
miR-9	20 patient sample	–	A549, NCI–H1299, HCC827, HEK293	↑ TGF-β ↓ E-Cadherin	↑ Cell Proliferation ↑ EMT	[65]
	30 paired of samples		A549, HCC827, NCI–H1299, HEK293, HBE, SK-LU-1, NCI–H460,	↓ SOX7	↑ Invasion ↑ Adhesion	[70]
miR-9-5p	62 paired samples	–	BEAS-2B, A549, SK-MES-1, H1299	↑ TGF-β ↑ SMAD2 ↑ SMAD3 ↓ TGF-βIIR	↑ Cell Proliferation ↑ Metastasis	[71]
miR-23a	–	–	PC9, RERF-LC-KJ, PC14, LC2/ad, A549, RERF-LC-OK, PC1, PC10, LK2, SQ5, BET2A	↑ TGF-β ↓ E-Cadherin	↑ EMT	[67]
miR-487b, miR-134, miR-655	–	–	PC3, RERF-LCKJ, LC2/ad, PC14, PC9ABC-1, RERF-LCMS, A549	↑ TGF-β ↓ MAGI2 ↓ PTEN	↑ EMT ↑ Drug Resistance	[72]
miR-1246	11 LC sample + 5 control sample	–	A549	↑ TGF-β ↑ Vimentin ↓ E-Cadherin ↑ β-Cadherin ↓ GSK-3β	↑ Metastasis ↑ Invasion	[73]
miR-181b-5p	–	Mice	A549, CD133+/CD326+	↑ TGF-β ↓ E-Cadherin	↑ EMT ↑ Metastasis	[68]
miR-27a	–	–	L132, H1703, A549, H157, H1299, H358	↓ TGF-β ↓ SMAD2 ↓ SMAD4	↑ Cell proliferation ↑ Invasion	[15]

miRNA-based therapeutics and for elucidating the roles of miRNAs in various diseases.

3. TGF-β signaling involved in hallmarks of lung cancer

TGF-β is a cytokine with many functions, including the control of growth, differentiation, and homeostasis in mammals. It also acts as a strong anticancer protein by inhibiting the uncontrollable growth of epithelial, endothelial, and hematopoietic cells. Resistance to TGF-β mediated growth arrest is a hallmark of human malignancies that arise due to alterations in the TGF-β axis [32,33]. TGF-β is normally involved in suppressing tumor growth, but genetic and epigenetic alterations work together to turn it into an activator of tumorigenesis and the spreading of cancer cells. Recent data suggest that TGF-β signaling has a vital role in directing the development of cancer hallmarks by cancer cells, however, the molecular pathways behind TGF-β′s oncogenic activities have yet to be fully elucidated [34].

According to recent data, increased vascular density, tumorigenesis, and a worse prognosis in NSCLC are linked with higher TGF-β levels in the carcinoma microenvironment [35]. The utilization of TGF-β′s effect on endothelial cells (EC) and elevation of growth factors like vascular endothelial growth factor (VEGF) are most likely the sources of its angiogenesis-inducing potential in cancer. For example, co-expression of VEGF and TGF-1 is common in cancers and other tissues where angiogenesis begins [36,37]. Furthermore, TGF-β increases matrix metalloproteinase 9 (MMP9) expression and encourages the production of fresh blood capillaries via a activin receptor-like kinase 5 (ALK5), creating a favorable atmosphere for endothelial cell migration (ECM), which is vital to creating blood vessels feeding the tumor tissues [38]. Additionally, Yoshimatsu and his team revealed that TGF-β has a negative effect on lymphangiogenesis [39]. TGF-β′s effect on angiogenesis is likely to be affected by many factors, such as the specific isoform of TGF-β, the stage of angiogenesis, and the presence of other pro- or anti-angiogenic factors.

On the other side, TGF-β possesses the capability to promote the evading process of the immune system [40], and natural killer group 2D ligands (NKG2DLs) may partake in that [41]. In lung tumor cells, promotion of TGF-β signaling may cause a reduction in NKG2DL production

Table 2
Roles of tumor suppressor miRNAs in TGF-β signaling pathway with their targeted genes and effects.

MiRNAs	Human study	Animal models	Cell line study	Mechanism Of Action	Effect	Ref.
miR-132	15 NSCLC patients	–	BEAS-2B, A549	↓ TGF-β ↓ SMAD2 ↓ Vimentin ↓ N-Cadherin	↓ EMT ↓ Migration ↓ Invasion	[81]
miR-422a	36 paired sample	25 BALB/c nude mice	BEAS-2B, A549, H358, H522, SPC-A-1	↓ TGF-β ↓ SMAD2 ↓ SMAD3 ↓ SULF2	↓ Cancer cell development ↓ EMT ↓ Invasion ↑ Apoptosis	[76]
miR-206	–	Rag2−/−:IL-2Rγc−/− mice	NCI–H1299, A549, NCI–H1975, HCC827	↓ TGF-β	↓ Tumor growth ↓ Metastasis	[82]
miR-107	–	–	HEK-293T, BESA-2B, H1299, A549, HCC827, 95-D, PC-9, H1975	↓ TGFβR2	↓ Proliferation ↓ Migration	[83]
hsa-miR-486-5p	65 paired sample	–	A549, BEAS-2B, H1299, H1650, SPC-A1, H460, H226	↓ SMAD2 ↓ TGF-β	↓ Migration ↓ Invasion	[84]
miR-142-3p	49 paired sample		A549, LTEP-a-2, H1299, 95C, H226	↓ TGFR1	↓ tumor growth	[85]
miR-203 miR-145	36 paired sample	–	A549, 95C	↓ TGF-β ↓ SMAD3	↓ EMT ↓ Tumor formation	[80]
miR-133a	32 paired sample	BALB/c nude mice	A549, H1299, BEAS-2B	↓ TGF-β ↓ SMAD3 ↓ LASP1	↓ Cell proliferation ↓ Tumor growth	[17]
miR-124	19 NSCLC patients	–	A549, H292	↓ TGF-β ↓ SMAD4 ↓ DNMT3s	↓ EMT	[86]
miR-196b	Cancerous and adjacent normal tissues	–	A549, H1650 H1299, WI-38, HEL-1	↓ TGF-β ↓ Runx2 ↑ E-Cadherin ↓ Vimentin ↓ N-Cadherin ↓ SNAIL ↓ ZEB1	↓ EMT ↓ Metastasis ↓ Invasion	[87]
miR-940	91 patients	–	A549, H226	↓ TGF-β ↓ SNAIL	↓ EMT ↓ Cancer Reformation	[77]
miR-145 miR-497	NSCLC tissues	–	A549, H1299	↓ TGF-β ↓ MTDH	↓ Migration ↓ Invasion ↓ EMT	[88]
miR-29c	20 paired sample	–	BEAS-2B, 95C, 95D, A549	↓ TGF-β ↓ Sp1	↓ EMT ↓ Metastasis	[89]
miR-22	Cancerous lung tissues	–	MRC-5, Anip973, AGZY83-a	↓ TGF-β ↓ SNAIL ↑ E-Cadherin ↓ N-Cadherin	↓ EMT	[90]
miR-195 miR-497	Tissue: (126 NSCLC specimens + 5 matched normal samples) Blood: (17 LC + 19 control samples)	nude mice	L132, A549, H157, H1299, H1703, HEK293T	↓ SMURF2 ↓ TGF-β1	↓ Tumorigenesis	[91]
miR-203 miR-145	36 paired sample	–	A549, H460, H1299, 95C, 95D, HBE	↓ TGF-β ↓ SMAD3	↓ EMT ↓ Invasion	[80]
miR-375	–	–	CCD-19Lu	↓ TGF-β ↓ P38 ↓ MAP2K6	↓ *Trans*-differentiation	[92]

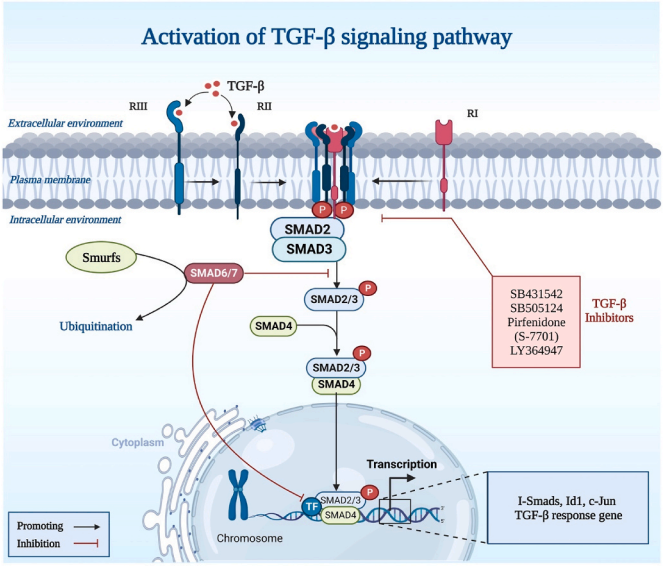

Fig. 1. TGF-β signaling cascade illustrated in a schematic format. TGF-β causes the phosphorylation of SMAD2/3, which is signaled by the binding of TGF-β to its receptors (TGF-β-RII and TGF-β-RIII) and this interaction causes the type I receptor (RI) to connect to the complex and undergo phosphorylation. SMAD2 and SMAD3 transcription factors are phosphorylated after being activated by this phosphorylation of the RI protein kinase. When SMAD2 or SMAD3 are phosphorylated, they connect to Smad4 and form a compound that translocated into the nucleus. The SMAD compound, in the nucleus, cooperates with other transcription factors (TFs) to modulate the influence of TGF-β on target genes. The phosphatase RI typically phosphorylates a certain region of Smad2 and Smad3, but the inhibitory Smad6 and Smad7 lack this region and prevent this from happening. Furthermore, the TGF-β pathway can be disabled by synthetic inhibitors, which work by blocking the receptor's enzymatic function.

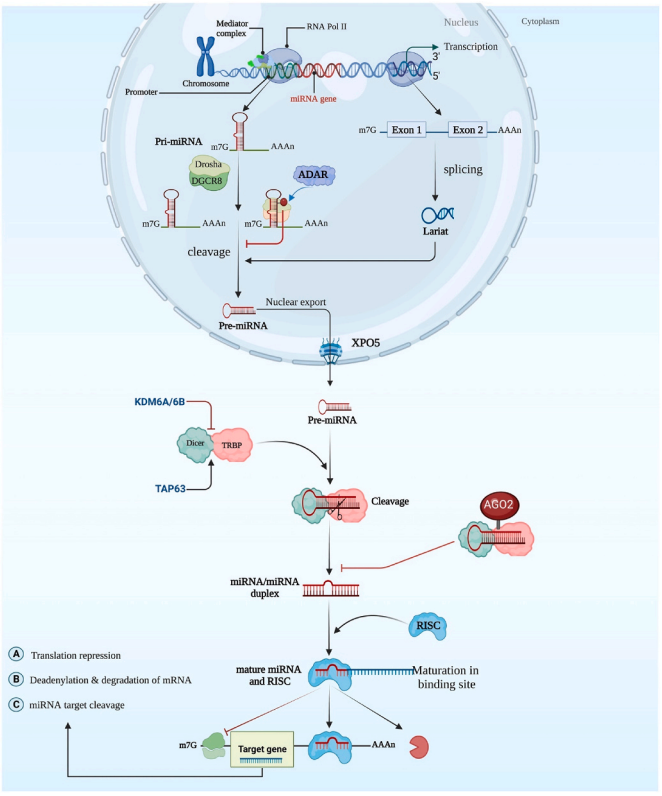

Fig. 2. The miRNA gene transcription by RNA pol-II within the nucleus is the first step in the canonical pathway of miRNA synthesis, which is described in the diagram. Drosha and DGCR8 digest the pri-miRNA transcript to generate the pre-miRNA, which is then transported by Exportin-5 to the cytoplasm. The pre-miRNA is cleaved into the mature miRNA duplex by Dicer and TRBP within the cytoplasm. One strand of the duplex is primarily selected as the mature miRNA, while the other is degraded after it has been loaded into the RISC. The mature miRNA then targets specific mRNA transcripts for degradation or translational repression.

and expression, which might be connected to higher matrix metalloproteinase 2 (MMP2) expression which is involved in the suppression process of immunity in the presence of lung tumors [42]. Not only that but it has also been revealed that through SMAD, TGF-β can exert immunosuppressive effects by phosphorylating SMAD3 [43,44], TGF-β induces the development of regulatory T-cells, when disabled as well as cytotoxic T-cells via FoxP3, a T-cell activity regulator [45]. Early work has revealed that malignant cells generating TGF-β produced lower cytotoxic T-lymphocyte (CTL) reactions than normal cells since it prevented T-lymphocytes from developing the high-affinity IL-2 receptor [46].

In addition, TGF-β can promote or suppress apoptosis, having highly context-dependent effects on the process. It's thought that the majority of its effects are believed to be pro-apoptotic in cancer cases, such as LC [47]. TGF-β induces the TGF-β inducible early response gene 1 (TIEG1), reducing B-cell lymphoma 2 (BCL2) levels, which inhibits the intrinsic mechanism of apoptosis in human cells [48].

Interestingly, in multiple ways, TGF-β can induce tumor production by encouraging EMT through the SMAD pathway. For example, TGF-β upregulates transcription factors that are involved in inducing the EMT process, such as drosophila embryonic protein SNAI1 (SNAIL) and zinc-finger E-box binding homeobox (ZEB) [49]. Additionally, TGF-β also activates via various non-Smad pathways, for instance, mitogen-activated protein kinase (MAPK), STAT3, NF-κB/Snail, Rho-like GTPase, and phosphatidylinositol-3-kinase (PI3K) pathways [50,51].

Overexpression of mesenchymal markers like N-cadherin, vimentin, and fibronectin leads to a reduction in E-cadherin level and a decline in polarity and tight junctions in the cells, as well as increased motility and invasiveness of the cells [52]. This makes it possible for metastases to grow in distant parts of the body because the cells can move through the extracellular matrix [53]. Furthermore, it has been found that EMT is directly linked to the growth of epithelial stem cells. Cancer stem cells (CSCs), also called "tumor-initiating cells" because they can start new tumors, are thought to be encouraged by TGF-β signaling with the transcription factors [54].

Additionally, TGF-β induces invasion, migration, and metastasis of cancer cells. Cells of LC typically metastasize to the brain, bones, and lymph nodes [55]. To facilitate cancer cell intravasation, TGF-β may boost the expression of the β3 integrin to promote cancer cell intravasation and by cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), raise regulatory T-cells to decrease $CD4^+$ T-cell proliferation, allowing circulating tumor cells (CTCs) of the lung to evade immune responses [56]. Further, through mothers against decapentaplegic homolog 3 (SMAD3), TGF-β can boost the expression of the dedicator of the cytokinesis 4 (DOCK4) gene, which in turn activates ras-related C3 botulinum toxin substrate 1 (Rac1). Therefore, Rac1 activation may promote the extravasation of cancer cells [57].

Additionally, it was revealed that TGF-β may stimulate the production of cyclin-dependent kinase inhibitors (CDKIs), including p15INK4B, p21CIP1, and p27KIP1, which, together with the inhibition of cyclin-CDK complexes, lead to cell cycle arrest in the G1 phase. In addition, it has been proven that TGF-β-blocking antibodies induce anti-tumor resistance and have clinical benefits in lung and other cancer patients [58].

Overall, TGF-β 's effects on cancer are diverse and context-dependent, and further studies are required to fully understand its function in cancer development and progression.

4. Roles of miRNAs in TGF-β signaling pathway in lung cancer

The TGF-β signaling pathway is a well-known regulator of cell division, proliferation, and apoptosis. Dysregulation of this pathway has been implicated in several human disorders, including cancer. TGF-β can play as a tumor suppressor and an oncogene, based on the cellular environment and the stage of the tumor. miRNA has a significant role in cancer progression [59] and can regulate the TGF-β pathway at multiple levels [60]. They can directly target or inhibit the expression of TGF-β pathway components, including TGF-β ligands, receptors, and downstream effectors.

4.1. Roles of oncogenic miRNAs in TGF-β signaling pathway

Oncogenic miRNAs are a class of miRNAs that induce tumor development and metastasis by targeting tumor suppressor genes [61,62]. In lung cancer, several oncogenic miRNAs have been identified that can dysregulate the TGF-β signaling pathway and induce cancer development. For instance, an oncogenic miR-3614-5p is frequently elevated in LC. miR-3614-5p can target several components of the TGF-β signaling, including phosphoglycerate mutase 1 (PGAM1) [63]. By suppressing the PGAM1, miR-3614-5p can activate TGF-β signaling and induce LC progression [63]. Another instance is miR-128-3p, which is also elevated in LC. miR-128-3p can reduce several Wnt/β-catenin and TGF-β pathway inhibitors, which results in the induction of mesenchymal and stemness-like properties [64]. In addition, the pseudogene MSTO2P binds with miR-128-3p in order to modulate the susceptibility of NSCLC (vascular endothelial growth factor C) to coptisine via TGF-β activation and VEGFC. Remarkably, VEGFC was able to recover miR-128-3p-attenuated NSCLC characteristics that were subjected to therapy with coptisine [16].

Likewise, by elevating miR-9's level and decreasing the levels of its target, E-cadherin, TGF-β1 caused EMT, invasion, and migration in NSCLC [65]. Moreover, by suppressing the expression of TGF-βR2, miRNA-9-5p encourages the cell proliferation, invasion, and metastasis of NSCLC cells [66]. Furthermore, through suppressing E-cadherin in LC cells, miR-23a controls TGF-induced EMT and may be effective as a potential therapeutic target in NSCLC [67]. In addition, through targeting of E-cadherin in both normal CD133+/CD326+ cells and A549 cells that exhibit hallmarks of CSLCs, miR-181b-5p controls TGF-1-induced EMT [68]. As a result, miR181b5p was demonstrated to be an innovative therapeutic target for NSCLC (Fig. 3a).

Overall, oncogenic miRNAs can activate the TGF-β signaling and lead to induce cancer progression and targeting these miRNAs may be a promising therapeutic method for LC treatment.

4.2. Roles of tumor suppressor miRNAs in TGF-β signaling pathway

Tumor suppressor miRNAs are a class of miRNAs that can suppress the development and proliferation of tumor cells [74]. Several tumor-suppressor miRNAs have been identified that regulate the TGF-β signaling in LC cells. These miRNAs can target several elements of the TGF-β signaling, such as TGF-β ligands, receptors, and downstream effectors. For instance, miRNA-132 is a well-known tumor suppressor miRNA that is downregulated in LC [75]. Elevated levels of miR-132 can target multiple elements of the TGF-β signaling, including TGF-β, SMAD2, vimentin, and N-cadherin [75]. By targeting these components, miR-132 can inhibit TGF-β signaling and suppress LC cell invasion, metastasis, and EMT. Similarly, by blocking the SULF2-dependent TGF-1/SMAD signaling pathway, miR-422a promotes apoptosis and suppresses cell proliferation, invasion, and migration in NSCLC [76]. Likewise, Jiang et al. demonstrated that by targeting Snail 3′-UTR mRNA, miR-940 can suppress TGF-β-induced EMT and cell invasion in NSCLC [77]. Moreover, by controlling LASP1 in vitro, miR-133a overexpression prevented the EMT and TGF-β/SMAD3 pathways [17]. Thus, miR-133a suppressed cell viability and tumor growth in NSCLC. Furthermore, Bai et al. revealed that by targeting RUNX2, the tumor suppressor miRNA-196b prevented lung cancer cells from proliferating and metastasizing [78]. These findings offered additional support for the treatment of lung cancer (Fig. 3b).

Interestingly, Yin et al. offered new approaches to demonstrating that miRNA-497 and miRNA-145 are promising therapeutic targets by demonstrating how they function as EMT suppressors via targeting MTDH in NSCLC [79]. Further, Hu et al.'s findings showed that the inhibition of SMAD3, miRNA-145, and miRNA-203 prevented TGF-induced EMT and cell invasion in NSCLC [80]. Their research revealed a method by which miRNAs regulate TGF-β-induced EMT and suggested a plan for NSCLC-targeted therapy.

Overall, tumor suppressor miRNAs play critical roles in regulating the TGF-β signaling pathway in LC. A possible therapeutic strategy for the management of LC may involve targeting these miRNAs.

5. TGF-β and therapeutic targets

Classical targeted therapies, including surgical, chemotherapy, immunotherapy, and radiotherapy, have made significant advances, but they still have drawbacks. For instance, low therapeutic indices, nonspecific targeting, the development of multiple drug resistance, and

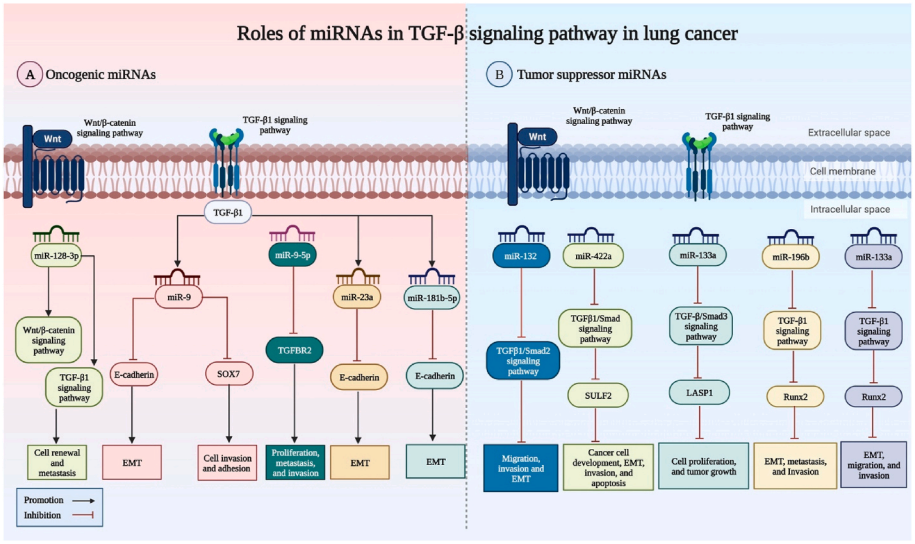

Fig. 3. Illustrates how the miRNA and the TGF-β signaling pathway interact with one another in lung cancer cells. (A) demonstrates the oncogenic miRNAs and how they affect the TGF-β signaling pathway, which encourages tumor cell proliferation, EMT, and metastasis. For instance, high levels of TGF-β result in the overexpression of both miR-181b-5p and miR-9 levels, which, by inhibiting E-cadherin activity, can accelerate the EMT process. (B) explains how several tumor suppressor miRNAs affect TGF-β signaling pathways by suppressing oncogenes. For example, high levels of miR-422a lead to suppression of the TGF-β/Smad signaling pathway, which results in inhibition of SULF2 production.

the therapeutic outcomes of a treatment can be altered by metastasis. Therefore, it is critical to develop a novel therapeutic strategy for the treatment of LC individuals.

MiRNAs and the TGF-β signaling pathway play essential roles in the growth and progression of lung cancer [10]. Targeting miRNAs or the TGF-β signaling pathway has the potential to be a promising therapeutic strategy for LC. For instance, restoring the expression of tumor suppressor miRNAs or suppressing oncomiRs could help restore normal gene expression patterns in LC cells. Inhibiting the TGF-β pathway could also be an effective strategy for treating LC, particularly in advanced stages of the disorder where TGF-β signaling encourages tumor growth and metastasis. By directly targeting MAGI2, Kitamura et al. showed that the miR-134/487b/655 cluster altered resistance to gefitinib and contributed to the TGF-β1-induced EMT phenomena. This suppression ultimately resulted in loss of PTEN stability in lung cancer cells [72]. Depending on the EMT phenomena, the miR-134/miR-487b/miR-655 group may represent a new treatment option in patients with advanced lung cancer.

For LC therapy, a number of strategies, including TGF-β pathway inhibitors and miRNA-targeted therapies, are being explored. MiRNA mimics or inhibitors, which can be administered directly to cancer cells using nanoparticles or other delivery systems, are the main strategy for miRNA-targeted therapeutics [93]. For instance, tumor suppressor miR-34a expression has been demonstrated to be controlled by the TGF-β signaling pathway in lung cancer, and miR-34a downregulation is likely to facilitate in TGF-β induced EMT and tumor progression. Hence, a phase I clinical trial is currently proceeding to study the safety and efficacy of a liposomal synthetic miRNA-34a mimic in combination with chemotherapy for the treatment of metastatic NSCLC [94]. Furthermore, antagomiRs are synthetic miRNA mimics that target miR-16, miR-34a, and miR-15b, which are currently inhibited in LC. In preclinical studies, antagomiRs showed anticancer efficacy and increased survival in lung cancer mouse models [95].

Using CRISPR/Cas9 gene editing technology to specifically remove or edit a particular miRNA gene in lung cancer cells is another strategy for targeting miRNAs [96,97]. This strategy is being explored in clinical trials for various cancers as it has demonstrated encouraging outcomes in preclinical studies. Other Cas proteins, such Cas12 and Cas13a, have the ability to be used practically for miRNA amplifications, therapeutic targets, and detection with great dependability, sensitivity, and high fidelity based on combining miRNA to crRNA [98,99].

In addition to miRNAs, several other targets in the TGF-β signaling pathway have been determined as possible therapeutic options in lung cancer, including TGF-β receptors, SMADs, and downstream target genes. Targeting these molecules may offer additional therapeutic strategies for LC treatment. For example, several anticancer drugs have been developed that target TGF-β signaling, such as carboplatin, a chemotherapeutic drug commonly used for patients suffering from lung cancer [100]. Carboplatin can express anti-cancer effects through several pathways, such as the inhibition of the TGF-β signaling pathway, in which oncogenic miR-21 is suppressed, resulting in upregulation of SMAD7 expression, to suppress receptor signaling mediated cell invasion in NSCLC [101] (Fig. 4a). Similarly, curcumin, which is isolated from *Curcuma longa,* is a natural polyphenol that has anti-tumor properties and suppresses tumorigenesis in various mechanisms through anti-metastasis and anti-proliferative properties against several cancers, including lung cancer [102]. Curcumin suppresses tumor development and promotes apoptosis in vivo and in vitro [103], and regarding TGF-β signaling status, it significantly inhibits the development of subcutaneous tumors. In H358 and A549 cells, curcumin reduced TGF-β induced Smad2/3 phosphorylation and transcription, but not in ACC-LC-176 cells [103]. Likewise, metformin, the safest and most commonly used treatment for type 2 diabetes mellitus (T2DM) [104], can exert its anti-cancer effects against lung tumors [105]. Metformin suppresses the TGF-β protein and lowers miR-21 production through the TGF-β signaling pathway, resulting in upregulation of *PTEN* and *SMAD7* protein expression [106] (Fig. 4b). This mediates the anti-angiogenic activity of metformin. Moreover, decitabine (DAC), an inhibitor of DNA methyltransferases, offers a variety of anti-cancer properties as it aims to cause apoptosis and cell cycle arrest by causing DNA hypomethylation [107]. As it renders cancer cells more sensitive to other therapies, slows the proliferation of tumor cells, and stimulates the immune system. DAC is proven to be more successful when used in conjunction with other treatments than when used alone [108]. DAC enhances the expression of miRNA-200c and miRNA-200a and can restrict the expression of ZEB1 and ZEB*2*, which results in the reduction of TGF-β1-induced EMT and metastasis in lung adenocarcinoma cells [109] (Fig. 4c). Additionally, cisplatin is another drug that can be noticeable in its chemotherapeutic

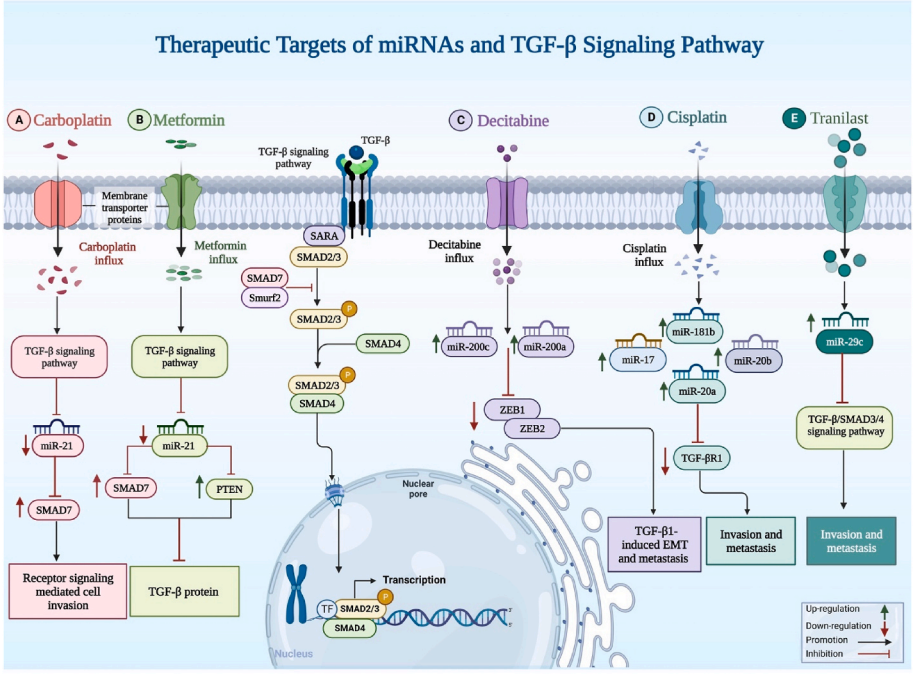

Fig. 4. The diagram represents the role of miRNAs and TGF-β signaling as promising therapeutic targets in the growth and progression of lung cancer. There are numerous approaches to treat lung cancer, such as TGF-β pathway inhibitors and miRNA-targeted therapies, are being studied. (A) carboplatin can disrupt the TGF-β signaling pathway, which upregulates the expression of SMAD7 and inhibits receptor signaling-mediated cell invasion in NSCLC. (B) Through the TGF-β signaling route, metformin inhibits the TGF-β protein and reduces the synthesis of miR-21, which increases the expression of the proteins PTEN and SMAD7. (C) The expression of ZEB1 and ZEB2 can be restricted by decitabine, which also increases the expression of miRNA-200c and miRNA-200a. This decreases TGF-β1-induced EMT and metastasis in lung cancer cells. (D) Despite being downregulated in cisplatin-resistant lung cells, miR-20a, miR-17, and miR-20b can inhibit TGF-β1, lower TGF-β signaling, reduce migration, and increase cisplatin sensitivity in chemotherapy-resistant cells.

action by influencing the expression of many miRNAs through various pathways, including the TGF-β signaling pathway [110]. MiR-181b has been revealed to directly target TGF-βR1, promoting cisplatin chemosensitivity and suppressing the invasion and metastasis of NSCLC. Wang et al. demonstrated that miRNA-181b is directly proportional to efficient cisplatin chemotherapy and inversely proportional to TGF-βR1 [111]. Although, in cisplatin-resistant lung cells, miR-20a, miR-17, and miR-20b are all downregulated [112], they can inhibit TGF-βR1, suppressing TGF-β signaling, decreasing migration, and enhancing cisplatin sensitivity in chemotherapy-resisting cells [112] (Fig. 4d).

Furthermore, Tranilast (TRN) is a low-toxic anti-inflammatory agent with anticancer potential [113]. It has the capacity to interfere with and alter the TGF-β signaling pathway, which prevents tumor cells from proliferating, invasion, metastasis; and promoting apoptosis by inhibiting *SMAD4* in LC cells [114] (Fig. 4e). Chemotherapeutic and immunotherapeutic drug efficacy is increased by TRN combination therapy [115]. Furthermore, TRN can activate the tumor suppressor miR-29c [116], and miR-29c can reduce resistance to cisplatin by inhibiting the TGF-β/SMAD3 [117], PI3K/Akt [118], and VEGFA [119] signaling pathways in NSCLC.

Overall, targeting miRNAs and TGF-β signaling pathways represents promising therapeutic strategies in LC, and more research is required to develop more specific and effective therapeutic agents targeting these pathways.

6. Conclusion and future perspectives

The function of miRNAs and TGF-β signaling in LC development and therapeutic targets is significant. MiRNAs play a crucial function in controlling the TGF-β signaling pathway and its downstream effectors, which are involved in various cellular processes that lead to LC progressions, such as the proliferation of cells, invasion, and migration.

Dysregulation of miRNAs and TGF-β signaling is associated with drug resistance and poor prognosis in LC patients. Therefore, targeting miRNAs and TGF-β signaling pathways holds great promise in order to create new therapeutic strategies for LC. Several miRNAs have been identified as potential targets for LC therapy, and preclinical research has proven the effectiveness of miRNA-based therapies in lung cancer models. Additionally, the development of small molecule inhibitors that target the TGF-β signaling pathway is ongoing, and these inhibitors may provide additional therapeutic options for LC patients.

However, there are several challenges to be addressed in this field, and the current research provides exciting opportunities to create more effective and personalized therapies for LC patients, which may ultimately improve patient outcomes.

Ethics approval and consent to Participant

Not applicable.

Consent of publication

Not applicable.

Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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Authors' contributions

BMH and MT wrote the draft and revised it. MT and AK designed and supervised the study. SJS, SRA, SM, HJH, and MFR collected the data and designed the figures and tables.

Declaration of competing interest

The authors declare they have no conflict of interest.

Data availability

Data will be made available on request.

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Abbreviation list

ALK5	Activin receptor-like kinase 5
BCL2	B-cell lymphoma 2
BMP	Bone morphogenetic protein
CDKIs	Cyclin-dependent kinase inhibitors
COX-2	Cyclooxygenase-2
CSCs	Cancer stem cells
CTCs	Circulating tumor cells
CTL	Cytotoxic T-lymphocyte
DAC	Decitabine
DOCK4	Dedicator of the cytokinesis 4
EC	Endothelial cells
ECM	Endothelial cell migration
EMT	Epithelial-mesenchymal transition
LC	Lung cancer
MAPK	Mitogen-activated protein kinase
miRNA	MicroRNA
MMP2	Matrix metalloproteinase 2
MMP9	Matrix metalloproteinase 9
MREs	miRNA response elements
NKG2DLs	Natural killer group 2D ligands
NSCLC	Non-small cell lung cancer
PGAM1	Phosphoglycerate mutase 1
PGE2	Prostaglandin E2
PI3K	Phosphatidylinositol-3-kinase
pre-miRNA	Precursor miRNA
pri-miRNA	Primary miRNA
Rac1	Ras-related C3 botulinum toxin substrate 1
RI	Type I receptor
RISC	RNA-induced silencing complex
SCLC	Small cell lung cancer
SMAD	Suppressor of mothers against decapentaplegic
T2DM	Type 2 diabetes mellitus
TFs	Transcription factors
TGF-β	Transforming growth factor-beta
TIEG1	TGF-β inducible early response gene 1
TRN	Tranilast
VEGF	Vascular endothelial growth factor
ZEB	Zinc-finger E-box binding homeobox

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