

# The Common miRNAs between Tuberculosis and Non-Small Cell Lung Cancer: A Critical Review

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Tuberculosis (TB) and non-small cell lung cancer (NSCLC) are two major contributors to mortality and morbidity worldwide. In this regard, TB and NSCLC have similar symptoms, and TB has symptoms that are identical to malignancy; therefore, sometimes it is mistakenly diagnosed as lung cancer. Moreover, patients with active pulmonary TB are at a higher risk of dying due to lung cancer. In addition, several signaling pathways involved in TB and NSCLC have been identified. Also, the miRNAs are biological molecules shown to play essential roles in the above-mentioned diseases through targeting the signaling pathways' genes. Most of the pathways affected by miRNAs are immune responses such as autophagy and apoptosis in TB and NSCLC, respectively. Several studies have separately investigated the expression of miRNAs profile in patients with NSCLC and infectious TB. In this critical review, we attempted to gather common miRNAs between TB and NSCLC and to explain the involved-pathways, which are affected by miRNAs in both TB and NSCLC. Results of this critical review show that the expressions of miR-155, miR-146a, miR-125b, miR-30a, miR-29a, and miR-Let7 have significantly changed in TB and NSCLC. The data suggest that miRNAs expression may provide a new method for screening or differential diagnosis of NSCLC and TB.

**Key words:** Tuberculosis; Non-small cell lung cancer; miRNA; Expression

## INTRODUCTION

Tuberculosis (TB) disease is considered as a major global public health threat (1, 2). Generally, TB affects the lungs, but the other parts of the body can also be affected. Accordingly, TB is caused by *Mycobacterium tuberculosis* (Mtb), which is a notorious intracellular pathogen resulting in millions of global deaths annually (3). Moreover, TB is one of the most important infectious diseases throughout history worldwide (4). So far, about one-third of the world's population has been infected by Mtb, and with respect to the reports, it accounted for about 1.6 million deaths in 2017 (5).

Lung cancer is a malignant tumor and uncontrolled cell growth of lung tissue, responsible for the highest rate of cancer-related mortality worldwide (6). Based on differences in histology, lung cancer is divided into small and non-small cell lung cancers (approximately 85%) (7, 8). In this regard, 25% of deaths due to cancers are related to non-small cell lung cancer (NSCLC) (9).

Micro-Ribonucleic Acids (miRNAs) are small, non-coding RNAs with a length of about 18-25 nucleotides (10, 11). These small molecules can regulate mRNA expression at the translational level or post-transcriptional level (12, 13). Correspondingly, several experimental studies

demonstrated that miRNAs participate in a wide range of physiological and pathological cellular processes such as cellular proliferation, metastasis, differentiation, and apoptosis through having interactions with target genes (14-20). In addition, miRNAs, as novel regulatory elements encoded within the human genome, are potentially oncomiRs or miR suppressors (21). Also, microRNAs were shown to play essential roles during the progress or suppression of human tumor development in various tissues (15, 22, 23). The role of miRNAs in human cancers is shown in Figure 1.

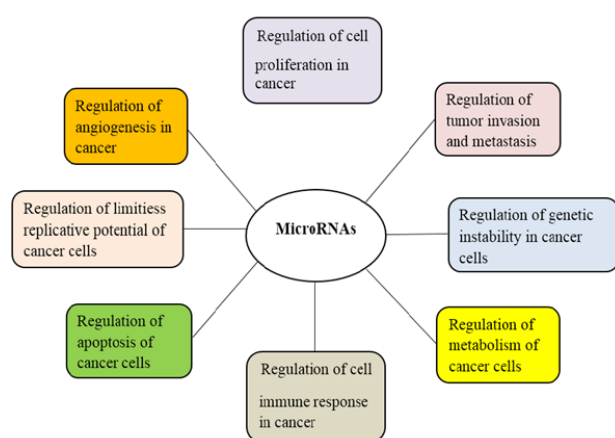


Figure 1. The role of microRNAs in human cancers

Although there have been relatively many studies conducted on the role of microRNAs in TB and NSCLC, no comprehensive study has been performed on the common microRNAs as well as the role of these microRNAs in these two diseases, so far. So, in this study, the common microRNAs between TB and NSCLC and their target genes, which can be used as serum markers for differential diagnosis of TB and NSCLC, were introduced.

This article research was performed in the PubMed and Scopus databases to find the involved-miRNAs in NSCLC and TB separately. Afterward, one thousand sixty-three research papers were found published from 2000 to 2019. The research papers were then studied and the associated miRNAs with NSCLC and TB were separately extracted. Therefore, the common miRNAs between TB and NSCLC were found and one hundred two articles were reviewed

by the authors. In all of the chapters, the alternation of miRNAs levels was mentioned, and the pathways and the genes affected by miRNAs were also explained.

#### The association between TB and NSCLC

Lung cancer is one of the most important causes of death worldwide (24). As many pathologists and clinical doctors have verified it, the connection between lung tuberculosis and lung or bronchial carcinoma certainly exists. Having TB prior to lung cancer increases mortality rates, so it is significantly correlated with mortality due to lung cancer, especially adenocarcinoma. Notably, it is much higher among smokers compared to non-smokers (25). Also, Human Papillomavirus (HPV), Immunodeficiency virus (HIV), and Hepatitis C increase the risk of cancers (26). TB has several symptoms similar to malignancy, so that, sometimes it can be mistakenly diagnosed as lung cancer (27). Moreover, some people after a relatively long period with delaying treatment and diagnosis and sometimes misdiagnosis of lung cancer and even taking anti-cancer drugs, are diagnosed with TB or as people with a history of TB who had lung cancer. A study in 2013, examined the relationship between TB and lung cancer, and it has been shown that TB is directly linked to lung cancer and its mortality, and this stance is intensified in smokers with TB. Also, Leung et al. demonstrated that mortality and morbidity due to lung cancer are associated with TB (28). In a population cohort study in 2011, the incidence of lung cancers between the two cohorts (subjects free from cancers and patients with newly diagnosed TB) was compared and the associated hazard of developing lung cancer was measured. Accordingly, this study demonstrated that the risk of lung cancer is higher in individuals with TB compared to normal subjects (29). Additionally, in countries where lung cancer is highly prevalent, TB patients are often misdiagnosed with the delayed treatment start and unnecessary diagnostic procedures (30). In a research paper Abd-El-Fattah et al. (31) performed microarray and qRT-PCR and revealed that

miR-21, miR-155, miR-182, and miR-197 are higher in the serum of lung cancer patients; however, miR-197 is higher in TB patients compared with healthy controls.

#### MicroRNAs in NSCLC

MicroRNAs are small molecules in the blood that play essential roles in the promotion or inhibition of some cancers like NSCLC (32, 33). The studies have demonstrated that microRNAs improve or inhibit the development of tumors by targeting the genes in biological pathways of cells (9). Also, microRNAs regulate the target mRNA translation into functional protein through binding to the 3'-untranslated region of target mRNAs (7, 34). In a research by Yan et al. (35), qRT-PCR technique was used and the correlation between the expressions of miR-99a and miR-224 was then analyzed in the serum of the NSCLC patients with clinicopathological features. Results showed that miR-224 is associated with NSCLC pathological stage, lymph node metastasis, and pathological grade; whereas miR-99 was shown to be associated with NSCLC pathological stage, lymph node metastasis, and tissue differentiation. Furthermore, miR-141, miR-200b, miR-193b, miR-200c, and miR-106b were the other NSCLC-related miRNAs overexpressed in NSCLC serum. In addition, Nadal et al. (36) analyzed the pathways upon the validation target genes and demonstrated that these miRNAs are associated with the pathways related to lung cancer biology such as MAPK, PI3K-AKT, p53, and neurotrophin signaling pathways. In another research performed by Jeon et al. (37) in situ hybridization, it was shown that the expressions of miR-224 and miR-520c are higher in metastasized lung tissues compared to primary tumors. Also, it was demonstrated that miR-224 and miR-520c enhance the metastatic potential of NSCLC by suppressing the endogenous Tumor Suppressor Candidate 3 (TUSC3) protein in A549 and H460 cells.

#### MicroRNAs in TB

Several miRNAs have been investigated to play a role in TB. In this regard, it was indicated that, the miRNAs affect the TB-related processes such as autophagy through

regulating multiple target genes and mRNA translation. Notably, autophagy is a process occurring in macrophages by Mtb, which plays a role in the activation of the innate and adaptive immune systems against intracellular bacteria. Also, one of the discovered TB-related miRNAs was miR-33. An in vitro study was conducted by Ouimet et al. (38) and showed that miR-33 is overexpressed in macrophages by Mtb and repress genes encoding key products in the autophagy pathway. Tu et al. (39) discovered miR-423-5p as another involved-miRNA in autophagy, which showed a higher expression in the serum of patients with TB compared to healthy controls. Moreover, miR-423-5p was discovered to target VPS33A gene to inhibit the autophagosome-lysosome fusion in macrophages. Also, miR-27a was identified to be involved in autophagy process. Accordingly, the level of this miRNA was shown to be upregulated in macrophages. In addition, it was shown that, miR-27a could inhibit the autophagosome formation as well as promoting the intracellular survival of Mycobacterium TB (40). The results of the previous studies provided evidence that miRNAs and their target genes can be used as serum markers for the diagnosis and treatment of TB and NSCLC.

#### The common microRNAs between TB and NSCLC

In this chapter, some of the common involved-microRNAs in TB and NSCLC were found which have been studied in the current papers (Table 1). Therefore, the expression alterations, gene targets, and the physiological and pathological mechanisms of some common microRNAs between TB and NSCLC were reviewed in this review paper. Herein, we attempted to focus on miRNAs that have been studied more and affect their gene targets and pathways, which have been discovered in the current papers. As a result of each part of the common miRNAs between TB and NSCLC (miR-155, miR-146a, miR-29a, miR-30a, miR125b, and Let-7), it can be said that miRNAs and their target genes can be used as therapeutic and diagnostic biomarkers in both TB and NSCLC, which may provide a new method for differential diagnosis of NSCLC and TB. The expression alterations, the gene targets, and

the function of miRNAs are summarized in table 1, table 2, and table 3, respectively.

**Table 1.** The common miRNAs between TB and NSCLC

MicroRNA	Reference	MicroRNA	Reference
miR-146a	(43, 44)	miR-let-7	(41, 42)
miR-146b	(44, 47)	miR-150	(45, 46)
miR-30a	(50, 51)	miR-21	(48, 49)
miR-155	(53, 54)	miR-17-5P	(39, 52)
miR-125a	(57, 58)	miR-29b	(55, 56)
miR-125b	(61, 62)	miR-29a	(59, 60)

**miR-155**

Notably, miR-155 is one of the miRNAs, which was shown to be involved in both NSCLC and TB diseases. Moreover, the role of miR-155 in TB and NSCLC diseases was through targeting the genes in biological signaling pathways (63, 64). Also, the expression of miR-155 was shown to be increased in TB and NSCLC; (53, 54) therefore, the results of the previous studies showed that miR-155 can be used as a prognostic biomarker (65). In this regard, Yang et al. (66) showed that, by the evaluation of miR-155, the recurrence and poor survival in NSCLC can be predicted. In another study performed by Donnem et al. (67) in situ hybridization, the prognostic impact of miR-155 in NSCLC was evaluated. Furthermore, they showed that the prognostic impact of miR-155 is significantly associated with the histological subtype and nodal status in NSCLC. Also, Wang et al. (68) performed a meta-analysis and calculated a pooled hazard ratio as well as analyzing the sensitivity. Moreover, they showed that the high expression levels of miR-155 are significantly correlated

with the worst NSCLC survival. On the other hand, in several studies, the pathways and the genes have been discovered, which are affected by miRNAs in TB and NSCLC. Accordingly, Xue et al. (53) revealed that miR-155 targets SOCS1, SOCS6, and PTEN genes. Thus, it promotes the development of NSCLC by downregulation of the above-mentioned genes. Also, in a study, the researchers showed the oncogenic act of miR-155 in NSCLC through targeting the PDCD4 gene and negatively regulating it (69). Additionally, in the previous studies performed on the role of miR-155 in TB, it was identified as a diagnostic biomarker that might present some potential signatures for the diagnosis of TB (70). Wagh et al. (71) demonstrated that the mycobacterium leads to the improvement of miR-155 expression alternation in TB patients (72). Autophagy was also described as a pathway, which causes the activation of the immune system against pathogens such as Mtb. Moreover, Etna et al. (73) identified the role of miR-155 in the autophagy and also discovered that the ATG3 gene is inhibited by miR-155 in autophagosomes. The apoptosis is another pathway that can be modulated by Mtb in the cells (74). Huang et al. (72) discovered that miR-155 targets the FOXO3 in the apoptosis pathway in monocytes, which results in the inhibition of apoptosis. Additionally, inactive TB, the long non-coding PCED1B-AS1 was shown to bind to miR-155 and to block it, which results in the regulation of the macrophage apoptosis and autophagy (75). In another study, miR-155 was shown to provide an effective adaptive immune response by promoting the survival and function of Mtb-specific T cells (76).

**Table 2.** The comparison of miRNAs expression in TB and non-small cell lung cancer

Common miRNAs between TB and NSCLC	Genomic location	Expression in NSCLC	Reference	Expression in TB	Reference
miRNA-155	21q21.3	High	(53)	High	(54)
miRNA-146a	5q33.3	High	(43)	Low	(44)
miRNA-125b	11q24.1	Low	(61)	Low	(62)
miRNA-30a	6q13	Low	(50)	High	(51)
miRNA-29a	7q32.3	Low	(59)	Low	(60)
miRNA-Let-7	9q22.32	Low	(41)	Low	(42)

### miR-146a

In addition, miR-146a was found to be altered in both TB and NSCLC. Accordingly, its expression was increased in NSCLC and decreased in TB (43, 44). In a research performed on the expression pattern of miR-146a in NSCLC patients, Wang et al. (43) performed qRT-PCR and observed that the expression of miR-146a has increased in NSCLC patients compared to the healthy controls. Therefore, it was identified as a diagnostic biomarker in NSCLC (43, 77). The results of several types of research have also shown that, in NSCLC, miR-146a plays essential roles in cell processes such as migration, apoptosis, and growth (78). Pang et al. (79) demonstrated that, when the JNK2 gene is targeted by miR146a, it increases the cisplatin sensitivity of NSCLC cells. In another study, Park et al. (80) performed a microarray and qRT-PCR and finally showed that miR-146a inhibits epithelial-mesenchymal transition in NSCLC cells by repressing the expressions of Insulin Receptor Substrate 2 (IRS2). Also, the results of another study showed that miR-146a plays a role in the development of the acquired drug resistance to the Cisplatin (DDP) in NSCLC cells by downregulating the cyclin J (81). Moreover, Zhang et al. (82) showed that miR-146a is a genetic factor that may be closely related to the susceptibility to pulmonary TB. Other scientists' studies performed in this regard recruited pulmonary TB patients with healthy controls. They concluded that genetic polymorphisms of miR-146a have significant roles in the risk of TB (83).

### miR-125b

Notably, miR-125b is another miRNA that was shown to be downregulated in both TB and NSCLC, which represents as another diagnostic biomarker (61, 62, 84). Li et al. performed real-time PCR and western blot on human NSCLC cells isolated from surgical tissues. Moreover, they identified tumor protein 53-induced nuclear protein 1 (TP53INP1) as a target of miR-125b. Thus, miR-125b promotes tumor metastasis by targeting this gene (85). Additionally, it was shown that the gene expression

pattern alterations of miR-125b results in the regulation of apoptosis signaling pathways such as the PI3K/Akt/GSK3beta and Wnt/beta-catenin (86). Also, Wang et al. (87) in their study revealed that miR-125b promotes the tumor invasion via the activation of the PI3K/AKT signaling pathway. Another study showed that, in NSCLC, miR-125b inhibits the Kinesin-1 light chain-2, which acts as a proto-oncogene (88). Another function of miR-125b is through the regulation of MMP-13. Yu et al. (61) revealed that the reduced expression levels of miR-125b lead to the increased MMP-13 expression levels, followed by the inhibition of invasive capabilities of cancer cells. Also, the effects of miR-125b expression on TB were assessed in some studies. Such studies showed that TNF is a target of miR-125b, which destabilizes the transcript of this gene (62).

### miR-30a

The lower expression of miR-30a in NSCLC patients compared to healthy controls was revealed in a study by Geng et al. (50) and higher expression of miR-30a in TB patients compared to healthy controls was revealed by Chen et al. (51). Notably, BCL11A is a target of miR-30a in NSCLC. MicroRNA-30a was shown to induce the increased expression levels of BCL11A in NSCLC tissues (89). Also, the inhibitory role of miR-30a in invasion and metastasis of NSCLC cell lines has been reported to be through targeting SNAIL (90). Additionally, the AEG-1, Snail, and Vimentin genes were investigated by Liu et al. (91), by binding to 3'-UTR of miR-30a and promoting the metastasis of NSCLC tumor in A549 cells. Wen et al. (92) used a luciferase reporter assay and demonstrated that miR-30a could suppress NSCLC cell proliferation through targeting IGF1R, which is in PI3K/AKT signaling pathway. Chen et al. (51) discovered the role of miR-30a in the immune response against Mtb in human macrophages through the inhibition of the autophagy-induced by Mtb.

### miR-29a

Hu et al. performed in vitro study and showed that miR-29a expression level is lower in NSCLC cells

compared to the healthy controls. Moreover, they identified LASP1 as a target gene of miR-29a and then explained that the overexpression of miR-29a decreases the growth of A549 cells in nude mice by targeting LASP1 (59). Additionally, several studies were conducted to indicate the role of miR-29a in TB. T cells were involved in the protection of the Mtb infected individuals from developing TB. Kleinstauber et al. showed lower expressions of miR-29a and miR-21 in TB patients. They observed no correlation between the expression of miR-29a and Interferon-gamma; however, a significant correlation was observed between the IL-17 positive T-cell clone's activation and miR-29a expression (60). Also, Afum-Adjei Awuah et al. (93) conducted a similar research, which demonstrated no correlation between the expression of miR-29a and Interferon-gamma.

#### miR-let-7

The expression level of miR-let-7 was shown to be lower in NSCLC patients compared to the healthy controls (41), which played a tumor suppressor role in NSCLC (94). Moreover, Yin et al. (95) demonstrated that the down-regulation of miR-let-7, up-regulation of LIN28A, and LIN28B expression resulted in the regulation of the single-cell proliferative capability of NSCLC cells. Thus, resistance to irradiation or cisplatin has been promoted. Also, miR-let-7 was shown to be altered in TB (96), and involved in immune response (42). Results showed that miR-let-7 is downregulated in Mtb-infected macrophages. Researchers indicated that miR-let-7 targets the TNFAIP3, as an inhibitor of the NF- $\kappa$ B pathway, which consequently results in the modulation of the immune response to Mtb infection of cytokines, including TNF and IL-1 $\beta$  (Table 3,4).

Table 3. The target genes of microRNAs in TB and NSCLC

Common miRNAs between TB and NSCLC	The target genes in NSCLC	References	The target genes in TB	References
miRNA-155	SOCS1	(53)	FOXO3	(72)
	SOCS6	(69)	ATG3	(73)
	PTEN		SHIP1	(62)
miRNA-146a	PDCD4			
	JNK2	(79)	COX-2	(97)
	IRS2	(80)	FLAP	
miRNA-125b	KLC2	(88)	TNF	(62)
	MMP-13	(61)		
miRNA-30a	MYBL2	(50)	ATG5	(51)
	BCL11A	(89)	beclin-1	
	SNAI1	(90)		
	AEG-1	(91)		
	Snail			
miRNA-29a	Vimentin			
	IGF1R	(92)		
	CDC42	(98)	Interleukin 17	(60)
	MTSS1	(99)		
miRNA-Let-7	LASP1	(59)		
	LIN28A	(95)	TNFAIP3	(42)
	LIN28B			

Table 4. The functions of each microRNAs in TB and NSCLC

MicroRNA	Function in NSCLC	Function in TB
miR-125b	Promotes tumor metastasis	Enhances TNF production
	Regulates apoptosis	
	Promotes tumor invasion	
miR-146a	Inhibits the migration	Involves in regulating inflammatory responses
	Induces apoptosis	
	Suppresses cell growth	
miR-155	Has oncogenic act	Has a role in autophagy
	Increases cell apoptosis	
miR-30a	Induces cell cycle arrest	Inhibits the autophagy
	Attenuates tumor growth	
	Suppresses cell proliferation	
miR-29a	Decreases the growth of A549 cells	Regulates T-cell clones activation
miR-Let-7	Tumor suppressor	Modulates the immune response to Mtb

## CONCLUSION

Several studies have been performed on the association between TB and lung cancer, and it was shown that TB is directly linked to lung cancer and its mortality. The risk of being affected by lung cancer is increased in patients with TB and having TB before lung cancer increases mortality rates. Additionally, TB has some symptoms similar to malignancy; therefore, sometimes it is mistakenly diagnosed as lung cancer. So, the identification of biological markers is necessary for differential diagnosis of TB and NSCLC (25, 27-29, 31, 100-102).

MicroRNAs are small molecules in blood of people, which play essential roles in biological pathways, through targeting the related genes. Several studies have been conducted on investigating the TB and NSCLC-related miRNAs, which finally resulted in identifying several miRNAs that play essential roles in signaling pathways of these two diseases. According to the results of this review, among all the miRNAs that were separately identified in TB and NSCLC, some of them were found to be common in both diseases. Additionally, the common microRNAs between TB and NSCLC have been shown to act through the same pathways in TB and NSCLC. Therefore, most of the pathways affected by miRNAs are immune responses such as autophagy in TB and apoptosis in NSCLC.

With a glimpse of studies on the assessment of miRNAs among TB and NSCLC patients, it is obvious that

these biological molecules can be used as diagnostic and therapeutic biomarkers for differential diagnosis, prognosis, screening, treatment strategies, and clinical management of these two diseases. The expression pattern of common miRNAs between TB and NSCLC should also be evaluated and then compared at the experimental level in a greater population that may be used as blood markers. So, it can prevent delayed diagnosis, delayed treatment, misdiagnosis, and getting lung cancer after TB. As well as the expression pattern of miRNA, target genes can also be evaluated to identify the action mechanisms of miRNAs.

## Abbreviation

SOCS1: Suppressor Of Cytokine Signaling; PTEN: Phosphatase and Tensin Homolog; PDCD4: Programmed Cell Death 4; JNK2: c-Jun N-terminal Kinase 2; IRS2: Insulin Receptor Substrate 2; KLC2: Kinesin Light Chain 2; MMP13: Matrix Metalloproteinase 13; MYBL2: MYB Proto-Oncogene Like 2; BCL11A: BAF Chromatin Remodeling Complex Subunit BCL11A; SNAI1: Snail Family Transcriptional Repressor 1; AEG-1: Astrocyte Elevated Gene-1; IGF1R: Insulin-Like Growth Factor 1 Receptor; CDC42: Cell Division Cycle 42; MTSS1: MTSS I-BAR Domain Containing 1; LASP1: LIM And SH3 Protein 1; LIN28A: Lin-28 Homolog A; FOXO3: Forkhead Box O3; ATG3: Autophagy Related 3; COX-2: Cyclooxygenase-2; FLAP: Five-Lipoxygenase Activating Protein; TNF: Tumor

Necrosis Factor; ATG5: Autophagy Related 5; TNFAIP3: TNF Alpha Induced Protein 3.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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