Review Article | Iran J Med Microbiol. 2023; 17(5): 492-504

10.30699/ijmm.17.5.492

Iranian Journal of Medical Microbiology | ISSN:2345-4342

A Systematic Review Study on the Role of Long Non-coding RNAs (lncRNAs) in *Mycobacterium tuberculosis*

Pegah Shakib[1], Rashid Ramazanzadeh[2], Reza Saki[3*], Razieh Amiri[3]

1. *Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*
2. *Department of Microbiology, Ardabil University of Medical Sciences, Ardabil, Iran*
3. *Department of Microbiology, Kermanshah University of Medical Sciences, Kermanshah, Iran*

ABSTRACT

Mycobacterium tuberculosis is the bacterium that causes tuberculosis. In this bacteria, long non-coding RNAs (lncRNA) can positively and negatively alter the expression of various genes through various mechanisms, such as activating transcription factors or binding to DNA targets of the chromatin complex. The current study's purpose was to review the lncRNAs in *M. tuberculosis.* The search was done with the keywords including lncRNAs, lncRNA, Long ncRNA, LincRNAs, Long ncRNA, long noncoding RNA, TB, Pulmonary Tuberculosis, Pulmonary TB, *Mycobacterium tuberculosis* in Pub Med, Web of Science Direct, Scopus, Scientific Information Databases, and Google scholar between 2000 and 2020. A total of 124 articles were found in PubMed, Science Direct, Scopus, Ovid, Cochrane, and Google Scholar, of which 20 papers were selected from the databases. In revising the title and abstract, 84 articles were excluded from our study. Finally, 19 articles were included in our study, comprising 4444 patients with tuberculosis. All studies were performed in China using the qRT-PCR method. The present study's results showed an acceptable association between lncRNA and SNP with tuberculosis and *M. tuberculosis*. Also, these regulatory factors play an essential role as diagnostic biomarkers and the development of new therapies.

Keywords: Long non-coding RNAs; Systematic Review; Biomarker; TB; lncRNAs

Received: 2023/05/25; **Accepted**: 2023/09/20; **Published Online:** 2023/11/29

Corresponding Information: **Reza Saki**, *Department of Microbiology, Kermanshah University of Medical Sciences, Kermanshah, Iran* Email: kasras47@yahoo.com

1. Introduction

Mycobacterium tuberculosis (*M. tuberculosis*) is the bacterium that causes tuberculosis, which has the highest mortality rate among infectious diseases. An estimated 10.4 million new cases are discovered each year, of which about 1.7 million result in death **(1)**. The resistance of tuberculosis-causing bacteria to anti-tuberculosis drugs is increasing as a global concern. MDR (multidrug resistance) and XDR (Extensively drug-resistant) resistors are also emerging today **(2)**. A routine laboratory test used to diagnose pulmonary tuberculosis is a microscopic smear. One of the limitations of this method is that it detects only half of the TB-related infections **(3)**. The standard gold method for identifying *M. tuberculosis* is culture, which has high sensitivity and specificity. However, the limitation of this method is that it takes at least a few weeks to reach the answer. Also, this method requires a lot of expensive laboratory infrastructure. In addition, it is challenging to collect sputum samples from children and adults **(4)**. In many cases, the diagnosis of extrapulmonary tuberculosis (EPTB) is delayed, failing the antibiotic course in some cases. Clinical findings are of little specificity, and tuberculosis tests such as Tuberculin skin test (TST), and Interferon Gamma Release Analysis (IGRA) may be erroneous; in addition, sites of extrapulmonary

tuberculosis infection may not be readily available for sample collection **(5)**. The current method for identifying *M. tuberculosis*, which responds in 3 to 5 days, is PCR, a fast and reliable method **(6)**.

The definition used for long non-coding (LNC) is long RNA, which is more than 200 nucleotides in length and does not translate into protein **(7)**. It is estimated that about 80% are involved in DNA sequences and are the primary targets for biomarkers and treatment **(8)**. Long non-coding RNAs (lncRNA) can positively and negatively alter the expression of various genes through various mechanisms, such as activating transcription factors or binding to DNA targets of the chromatin complex through the formation of Heterogeneous nuclear ribonucleoproteins (hnRNPs) **(9)**. However, many studies have shown that lncRNAs are involved in various biological processes such as transcription, splicing, protein synthesis, cell structure integration, cell cycle, apoptosis, stem cell pluripotency, reprogramming, and heat shock response **(10)**. Early detection of tuberculosis is necessary to prevent its spread within the community. Therefore, the presence of biomarkers for early detection of tuberculosis is essential to prevent its progression in the individual and society. Past studies have shown the potential value of microRNA (*miRNA*) lncRNA, and several other proteins as biomarkers for diagnosing tuberculosis **(11, 12)**. LncRNA can be detected in the blood of people with tuberculosis, which is a new way to diagnose people with tuberculosis. The aim of this systematic review was to clarify the role of lncRNAs in *M. tuberculosis*.

2. Materials and Methods

2.1. Search strategy

In the current systematic review study, we searched with the keywords lncRNAs, lncRNA, Long ncRNA, LincRNAs, Long ncRNA, long noncoding RNA, Tuberculosis, TB, Pulmonary Tuberculosis، Pulmonary TB, *Mycobacterium tuberculosis* in PubMed, Science Direct, Scopus, Ovid, and Cochrane, and Google scholar between 2000 and 2020. There was no limit to the year the article was published. The language of the article search was limited to English. In order not to lose any of the reference articles, the obtained articles were also searched.

2.2. Data Extraction and Quality Assessment

Each study was reviewed, and information including first author name, year of publication, country, number of samples, study groups, diagnostic method, long non-coding RNA name, and gene expression was extracted from each article. All duplicate articles, papers in languages other than English, Review articles, and Case Reports were excluded from our study (Figure 1). The quality of all obtained articles was evaluated by criteria (QUADAS-2).

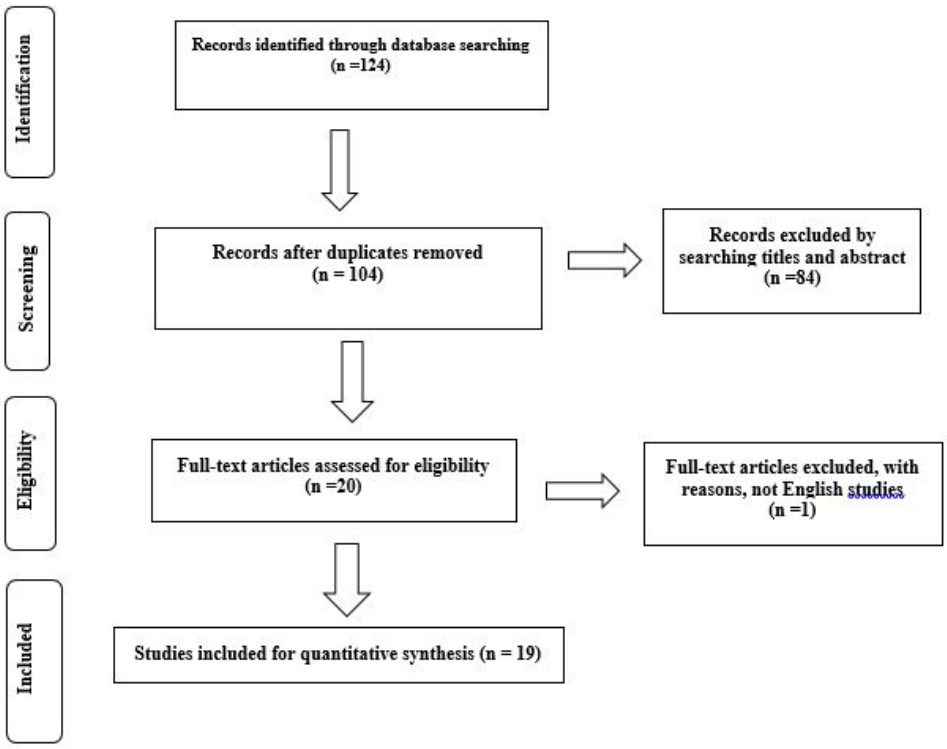

Figure 1. Flow chart of the literature search and selection

3. Results

3.1. Study Characteristics

A total of 124 articles were found in PubMed, Web of Science Direct, Scopus, Scientific Information Databases, and Google Scholar, of which 20 papers were shared between the databases. In revising the title and abstract, 84 articles were excluded from our study. Finally, 19 articles were included in our study, which included 4444 patients with tuberculosis. All analyses were performed in China using the qRT-PCR method. Several LNCs for which no information was available were collected through contact with the corresponding author for their information (Table 1). In addition, several microscopically studied articles did not have the names of all their LNCs in the article, so in this systematic review, we only mentioned the names of those LNCs that were in the full text of the article.

Table 1. Summary of all studies used in the present study

First Author	Year	Region	Detection Methods	Sample	Ref
Qian Wu	2019	Western Chinese	iMLDR	peripheral blood	**(13)**
Zhong-liang Chen	2017	China	microarray and RT-qPCR	plasma	**(14)**
Hao Bai	2018	West China	RT-qPCR	whole blood	**(15)**
Yurong Fu	2017	China	microarray and RT-qPCR	whole blood	**(16)**
Jianan He	2017	China	microarray and RT-qPCR	plasma	**(17)**
Shuying Huang	2018	China	RT-qPCR	peripheral blood	**(18)**
Hong Yan	2019	China	microarray and RT-qPCR	Peripheral blood	**(19)**
Jiajia Song	2019	West China	iMLDR	peripheral blood	**(20)**
Mingying Li	2019	China	qPCR	peripheral blood	**(21)**
Jing Li	2017	West China	RT-qPCR	whole blood	**(22)**
Jiajia Songa	2019	China	iMLDR	peripheral blood*	**(23)**
Zhengjun Yi	2014	China	microarray and RT-qPCR	whole blood	**(24)**
Zhenzhen Zhao	2017	West China	iMLDR	whole blood	**(25)**
Zhenzhen Zhao	2019	West China	iMLDR،multiplex PCR	peripheral blood	**(26)**
Yurong Fu	2017	China	microarray and RT-qPCR	Peripheral blood	**(27)**
Yang Wang	2015	China	qPCR،flow cytometry،microarray	Peripheral blood	**(28)**
LiMin Wang	2018	China	RT-qPCR	peripheral blood	**(29)**
Xing Zhang	2019	China	qPCR	peripheral blood	**(30)**
Zhi-Bin Lia	2020	China	microarray،qpcr	Plasma	**(31)**

*i MLDR: improved multiplex ligation detection reaction/ RT-qPCR: reverse transcription-quantitative polymerase chain reaction

3.2. LncRNAs as Potential Biomarkers in *M. tuberculosis*

As shown in Tables 2 and 3, 20949 lncRNAs and 12204 mRNAs were conducted to study and 5 of them were validated by q-PCR method. Compared with the group whose TB was not treated and the treated individuals had downregulated expression levels of uc.48 + and NR_105053, compared with healthy controls and those treated with tuberculosis, the expression level of uc.48 and NR_105053 was upregulated. Untreated, the expression level of the two LNC uc.48 and NR_105053 was upregulated **(31)**. In another report, the expression level of LINC00152 was much lower in people with TB than in healthy people. Also, SNP rs80292941 was introduced as a biomarker and predictor of side effects of hepatotoxicity due to anti-TB drugs **(22)**. In another study, two LNCs, lnc-AC145676.2.1-6 and lnc-TGS1- were observed in 467 patients with tuberculosis. These two LNCs were down-regulated in people with tuberculosis, which means that these two LNCs were involved in the development of tuberculosis. They can be mentioned as biomarkers **(15)**. This study showed

that low expression of lnc-TGS1-1 is closely related to thrombocytopenia in patients treated with anti-TB drugs **(15)**. The lnc-TGS1-1- rs4737420 variant is also associated with a reduced risk of leukopenia in these individuals **(15)**.

In another study with a difference in expression level (DE) of 449 LNC, DE 6 were randomly selected for Validation by Real-time PCR using HSPA4-5: 1 and lnc-ARG2-3: 1, downregulated and LNC-HNRNPU. -1: 7, CD27-AS1: 16, lnc-ABT1-3: 5, lnc-CCNT1-1: 1, have been upregulated in patients with pulmonary tuberculosis **(30)**. This study, also showed that lnc-GBP4-1-1 and lnc-GBP7-1-2 regulated the guanylate binding protein (GBP4) and GBP5 genes, indicating the regulatory role of LNC **(30)**. He *et al.* examined three groups of people with tuberculosis, CAP, and CG, of which 3 were tested by microbial method and 50 by qRT-PCR. (6 to up-regulated and 6 to down-regulated) were examined and analyzed (Tables 2 and 3), these two LncRNA can be selected as biomarkers **(17)**. It was found that ENST00000427151 targets cd81 antigen and ENST00000354432 sodium/glucose transporter (SLC5A10) (17). In another study, the expression of various mRNA and LncRNA in peripheral blood mononuclear cells (PBMCs) was examined. The subjects were divided into three groups: Drug-resistant individuals (MDR-TB), Drug-sensitive individuals (DS-TB), and healthy controls 6 LncRNA were randomly validated. Four LncRNA had similar expression in the two groups with TB compared with the healthy control group. It was also found that 2 LncRNA (CTD-2331D11.3 and AC079779.5) are involved in the pathogenesis of MDR-resistant individuals **(19)**.

Gene Ontology (GO) analysis in this study in MDR subjects showed that up-regulated mRNAs and their down-regulated mRNAs are involved in T-cellular responses and immune responses **(19)**. In a study that examined 844 B-cell lncRNA in people with TB by microarray, ENST00000505706 and ENST00000562027 had the highest and lowest expression, respectively. Bioinformatics analysis such as GO found that increased B cell expression in TB + individuals induces immune and molecular responses to bacteria. T-cells, NK-cells, and the processing and presentation of antigens are mainly related to the low expression of mRNAs **(16)**. Four lncRNA was validated by qRT-PCR as shown in Tables 1 and 2. In this study, for the first time, it was shown that up-regulated, XLOC_012582 lncRNA causes high expression of the SOCS3 gene, which is a negative regulator of cytokine responses, thus determining the relationship between mRNA and lncRNA expression **(16)**. In a study that looked at 511 lncRNA and 411 mRNA in the blood plasma of people with TB, 163 were up-regulated, lncrna348 were down-regulated, and 6 of them were confirmed by qRT-PCR, of which 4 lncRNA could be used as a biomarker **(14)**. This study's, coding non-coding co-expression (CNC) analysis showed that expression levels NR_038221 and ENST00000422183 were positively correlated with IL6ST and negatively correlated with TLR6. NR_003142 and ENST00000570366 are positively associated with MT1H and IL5, respectively. Also, the association of the expression level of lncRNA-NR_038221, which qRT-PCR confirmed, was found to target genes such as TLR6, NOD2, and CD3E. Other bioinformatics analyses, such as GO, showed that differences in the expression of different mRNAs were positively and negatively associated with INFG, TH1, and T-cell selection cell responses. KEGG analysis also demonstrated the association of different Jak-STAT signaling pathways, TCR, with down-regulated mRNAs, so that T cell activation in patients may be related to lncRNA dysregulation **(14)**. It has been described that AC079767.4 lncRNA is a robust biomarker for the diagnosis of tuberculosis, and this lncRNA can also be used for therapeutic purposes. Rs 1055229 is closely related to the ESR test for follow-up of TB patients. Also, the rs12477677 minor allele is closely related to fever, one of the most common symptoms of TB, and this SNP has a protective effect on TB progression. This study showed that AC079767.4 lncRNA SNP could be used for diagnostic and therapeutic purposes **(25)**. Analysis (lncRNA) of LOC152742 and high expression of this lncRNA in people with pulmonary tuberculosis showed that this lncRNA could be helpful as a biomarker for diagnosis **(29)**. Five polymorphisms of the RP11-37B2.1 LncRNA gene were examined in a large study that linked the risk of tuberculosis. Among them, only Snp rs39509 was statistically justifiable **(23)**.

3.3. Role of lncRNAs in Therapeutic Targets and Immune Responses to *M. tuberculosis*

The innate and acquired immune systems are involved in the body's immune response to tuberculosis so cd4 and cd8 cells play an essential role in the acquired immune system and are particularly important in combating MTB. Also, tcd8 cells, which are less critical than tcd4 cells against *M. tuberculosis*, can fight this bacterium in different ways **(32, 33)**. Studies have shown that lncRNA plays a critical role in modulating immune responses, including T lymphocyte responses, which include activation and differentiation **(34, 35)**. In one study, 30586lncrna and 20109 mRNA were examined in tcd8 cells, and 328 lncRNA expressed differences, 4 of which were validated with qRT-PCR (Tables 2 and 3) **(16)**. LOC152742 and TTTY15 had the highest and lowest expression, respectively, so this lncRNA can be considered as promising biomarkers. Two of the lncRNA that had expression changes in peripheral

blood tcd8 and tcd4 cells were ENST00000435287 and NR_024334. Gene ontology analysis in this study showed that in tcd8 cells with TB, processes such as extracellular matrix, apoptotic signaling pathways, cell migration and up-regulated cellular component movement, and signaling pathways such as cellular and inflammatory responses, defense responses and system regulation has had down-regulated safety. Another analysis called KEGG showed that CAMP, TGFB and calcium signaling pathways were up-regulated and down-regulated mRNAs in the process of antigen processing and presentation, NK-cell and cytotoxicity **(16)**. This study also showed that up-regulated lncRNA XLOC_014219 causes down-regulation of the gene encoding the protein HMOX1, impairs the function of tcd8 cells in patients with tuberculosis, which requires further investigation (16). In another study, the expression of mRNA and lncRNA in tcd4 cells in three groups (active TB, latent TB, healthy control) was examined by the microbial method. This study found that the expression level of two lncRNA, NR_024586 and ENST00000431999, which were down-regulated, was closely related to the genes encoding MLL5 and CYP1B1 proteins. Most lncRNA whose expression was different of the intergenic class (50%). Forty-one lncRNA differed in expression between the three groups, and 23 differed in comparison with active TB, latent TB, and healthy control. lncRNA NEAT1 was one of those reported to have down-regulated LncRNA compared with healthy individuals, which may indicate neat1 in response. Host immunity against pathogens is involved **(24)**. Macrophages play a vital role in the immune system against Mycobacterium tuberculosis. LncRNAs are also effective in regulating macrophage responses against microbes. In the study of lncRNA profile expression, PCED1B-AS1 lncRNA expression was analyzed in macrophages, which showed the expression level of PCED1B-AS1 in monocyte cells of people with active tuberculosis-healthy individuals decreased **(21)**. In this study, using a flowcytometry with PCED1B-AS1 suppressor in macrophages, it reduced TNF-a expression and resulted in macrophage apoptosis, and it was shown that PCED1B-AS1 reduction suppressed FOXO3 and RHEB genes. Also, electron microscopy and immunofluorescence methods showed that with the downregulation of PCED1B-AS1, autophagy and phagosome formation occur **(21)**. Another finding of this paper was that a microRNA called mir-155 increased its expression in monocytes of people with TB, so they found that mir-155 binds to PCED1B-AS1 and down-regulates this lncRNA **(21)**. In another study, CD244 expression levels were examined by flow cytometer in tcd8 cells, which were found to be active in people with tuberculosis. In TCD8 cells, cd244 has up-regulation. Therefore, it has been suggested that the CD244 signaling pathway hurts EZH2 and that EZH2 itself has an effect on inhibiting INFG and TNF-A production. This study found that lncRNA-BC050410 lncRNA-CD244 has a higher expression in CD244 + CD8 + T cells and is positively correlated with the CD244 signaling pathway in TB + individuals **(28)**. Up-regulation or down-regulation o lncRNA-CD244 is controlled by the INFG and TNFA locus suppressing or producing **(28)**. Therefore, this study suggests that lncRNA-CD244 affects the immune response against MTB in CD8 + T cells by acting EZH2, which affects the production of IFN-γ and TNF-α **(28)**.

Evidence suggeststhat lncRNA plays an important role in regulating the innate immune response in patients with tuberculosis. In a study of NEAT1 lncRNA in PBMC cells, people with tuberculosis were found to have increased NEAT1-1 and NEAT1-2 in patients with tuberculosis. It was found that the expression levels of NEAT1-1 and NEAT1-2 decreased after six months of treatment and were no different from healthy individuals, but in people with a recurrence of TB, this lncRNA expression did not change compared to new cases. This study used si-RNAs to suppressNEAT1 and showed that the cytokine IL-6 was reduced, but TNFα was not altered **(18)**.

3.4. Correlation of lncRNA with Susceptibility, Clinical Characteristics, and Adverse Drug Reactions

Research has shown that one of the significant challenges facing physicians is the development of adverse reactions (ADRs) caused by treatment with anti-TB antibiotics. It is important to note that one of the leading causes of failed treatment is resistance to treatment and even death of ADRs. In addition, there is a strong association between genetic variants and TB susceptibility, and increases in these SNPs are associated with ADRs induced by Anti-TB therapy. Therefore, the study of SNPs and genetic variants is critical. A study examined the relationship between lnc-HNF1B: 3: 1 genetic variant with clinical features and symptoms (fever, night sweats, weight loss, etc.) in patients with pulmonary and extrapulmonary tuberculosis as well as side effects (ADR) of drugs Anti-TB was reviewed. In this study, patients with rs12939622 and rs4262994 SNPs with AA genotype were more prone to fever symptoms than others. In connection with drug side effects, they examined seven side effects (anemia, CHD, thrombocytopenia, hyperbilirubinemia, leukopenia, AKI). They found that rs2542670 SNP was statistically associated with thrombocytopenia, leukopenia, and chronic renal problems. SNP Rs2688 protects against MTB in laboratory models **(13)**. In another study by the same people who performed the ACN79767.4 lncRNA SNPs, the association of these SNPs (rs10178277, rs12477677, rs1055228 and rs1055229) was evaluated by multiplex PCR with anti-tuberculosis

drug-induced hepatotoxicity (ATDH). Unfortunately, ATDH is the most common side effect seen in patients treated with anti-TB drugs. There was an association between rs1055229 and ATDH. Also, the CT / TT genotype of this SNP was associated with the development of hepatotoxicity problems and their incidence (26). In another study of 554 TB patients, four SNPs and six lncRNA haplotypes of RP11-37B2.1 were examined. One of the results was no significant association between the 6 haplotypes. (CCC, TTT, CTT, CTC, CCT, and TTC) and no TB. Of the 4SNPs, only Rs218916 was strongly associated with thrombocytopenic problems in drug-treated individuals, and there was also a weak association between rs218921 and hepatotoxicity (20).

Table 2. Characteristics of studied LncRNA related to TB

Sequence	Gene	location	Class	Related diseases	Ref
ENSG00000250985	lnc-HNF1B-3:1	chr17	intronic	27	**(13)**
NR_038221	LINC00870	chr3	intergenic	0	**(1)**
NR_003142	SNHG9	chr16	intergenic	19	**(14)**
ENST00000570366	lnc-B3GNTL1-1	chr17	intergenic	27	**(14)**
ENST00000422183	GAS5:34	chr1	antisense	23	**(14)**
ENST00000568177	lnc-CKB-1	chr14	bidirectional	44	**(14)**
ENST00000449589	GAS5:8	chr1	antisense	5	**(14)**
lnc-AC145676.2.1-6	Lnc-AC145676.2.1-6	chr7	intergenic	58	**(15, 26)**
lnc-TGS1-1	lnc-TGS1-1	chr8	antisense	15	**(15, 26)**
ENST00000354432	lnc-FAM83G-1	chr17	antisense	56	**(17)**
uc004cov.4	NA	NA	NA	NA	**(17)**
NR_044997	HCG25	chr6	NA	97	**(17)**
ENST00000427151	CD81-AS1:3	chr11	antisense	27	**(17)**
ENST00000442037	H19:17	chr11	intergenic	41	**(17)**
ENST00000546607	GLYCAM1	NA	NA	NA	**(17)**
ENST00000428188	IL1R1-AS1	chr2	antisense	0	**(17)**
TCONS_00019972	lnc-FAT3-2	chr11	intergenic	11	**(17)**
TCONS_00004316	lnc-REG1B-3:1	chr2	intergenic	25	**(17)**
ENST00000568137	lnc-ZFHX3-27	chr16	bidirectional	16	**(17)**
ENST00000584688	lnc-SPACA3-1:1	chr17	antisense	28	**(17)**
TCONS_00019584	lnc-SOX6-1:1	chr11	intergenic	26	**(17)**
NEAT1:1	NEAT1	chr11	intergenic	70	**(18)**
LOC0101929497	NA	NA	NA	NA	**(19)**
LINC01496	LINC01496	chrX	intergenic	28	**(19)**
BRE-AS1	BRE-AS1	chr2	intronic	29	**(19)**
CTC518B2.10	NA	NA	NA	NA	**(19)**
CTD-2331D11.3	lnc-COX7C-9	chr2	intergenic	2	**(19)**
AC079779.5	lnc-FAM150B-2	chr2	intergenic	844	**(19)**
RP11-37B2.1(ENSG00000251136)	lnc-NBN-1:1	chr8	bidirectional	243	**(20)**
PCED1B-AS1	PCED1B-AS1	chr2	intergenic	286	**(21)**
LINC00152	CYTOR	chr2	intergenic	192	**(22)**
RP11-37B2.1	lnc-NBN-1	chr8	bidirectional	243	**(23)**

Sequence	Gene	location	Class	Related diseases	Ref
ENST00000429730	LINC01857(lnc-CCNYL1-1:1)	chr2	intergenic	7	**(24)**
ENST00000457582	DEFA8P	chr8	Intergenic	0	**(24)**
uc011ncc.1	DDX11L	chrY	Intergenic	0	**(24)**
chr2:192293450-192304436	lincRNAOBFC2A-4	chr2	Intergenic	0	**(24)**
AC079767.4(ENSG00000224137)	lnc-CCNYL1-1(LINC01857)	chr2	intergenic	7	**(25)**
CTD-2281E23.2-001	lnc-CLN8-11	chr8	intronic	59	**(16)**
RP11-298J20.3	lnc-CTBP2-1	chr10	antisense	48	**(16)**
AC016683.6	PAX8-AS1	chr2	antisense	217	**(16)**
RP11-382A18.1	lnc-FAM84B-15	chr8	antisense	34	**(16)**
RP11-99H8.1	lnc-PTGER3-1	chr1	intergenic	15	**(27)**
ENST00000507373	SH3TC2-DT	chr5	intergenic	5	**(27)**
RP1-90G24.6	lnc-RFPL3-2	chr22	intergenic	23	**(27)**
TCONS_00024847	lnc-IRX5-2	chr16	intergenic	0	**(27)**
LOC152742	lnc-CPEB2-18	chr4	intergenic	0	**(29)**
Lnc-HNRNPU-1:7	lnc-HNRNPU-1	chr1	intronic	36	**(30)**
CD27-AS1:16	CD27-AS1	chr12	antisense	15	**(30)**
lnc-ABT1-3:5	lnc-ABT1-3	chr5	intergenic	21	**(30)**
lnc-CCNT1-1:1	lnc-CCNT1-1:1	chr12	intronic	39	**(30)**
lnc-ARG2-3:1	lnc-ARG2	chr14	intergenic	0	**(30)**
lnc-HSPA4-5:1	lnc-HSPA4-5	chr5	intergenic	0	**(30)**
T150805	NA	chr17	Intergenic	NA	**(31)**
ENST00000416708	lnc-IGFBP1-2	chr7	intergenic	16	**(31)**
NR_105053	PSD2-AS1	chr5	intergenic	0	**(31)**
NR_126366	PIK3CD-AS2	chr1	antisense	47	**(31)**
T274995	NA	chr4	Intergenic	NA	**(31)**
uc.48+	NA	chr2	Intronic antisense	NA	**(31)**
lncRNA-CD244	NA	NA	NA	NA	**(28)**

NA: Not Available

Table 3. Association between expression lncRNAs with TB

seq/gene	sample(patient/HC)	variation	Change of expression	ref
Lnc-HNF1B-3:1(ENSG00000250985)	526/561	1	-	**(13)**
NR_038221	52	1	up-regulated	**(14)**
NR_003142	52	3	up-regulated	**(14)**
ENST00000570366	52	1	up-regulated	**(14)**
ENST00000422183	52	1	Down-regulated	**(14)**
ENST00000568177	52	1	no reactive	**(14)**
ENST00000449589	52	1	no reactive	**(14)**
lnc-AC145676.2.1-6	467/473	3	down-regulated	**(15, 26)**

seq/gene	sample(patient/HC)	variation	Change of expression	ref
lnc-TGS1-1	467/473	1	down-regulated	(15, 26)
ENST00000354432	50	1	up-regulated	(17)
uc004cov.4	50	1	up-regulated	(17)
NR_044997	50	6	up-regulated	(17)
ENST00000427151	50	1	up-regulated	(17)
ENST00000442037	50	1	up-regulated	(17)
ENST00000546607	50	1	up-regulated	(17)
ENST00000428188	50	1	down-regulated	(17)
TCONS_00019972	50	1	down-regulated	(17)
TCONS_00004316	50	1	down-regulated	(17)
ENST00000568137	50	1	down-regulated	(17)
ENST00000584688	50	1	down-regulated	(17)
TCONS_00019584	50	1	down-regulated	(17)
NEAT1	106	4	up-regulated	(18)
LOC0101929497	50/50	1	down-regulated	(18)
LINC01496	50/50	1	down-regulated	(18)
CTC518B2.10	50/50	1	down-regulated	(18)
BRE-AS1	50/50	1	up-regulated	(18)
CTD-2331D11.3	50/50	1	up-regulated	(18)
AC079779.5	50/50	28	up-regulated	(18)
RP11-37B2.1(ENSG00000251136)	554/561	10	no reactive	(20)
PCED1B-AS1	20/20	12	down-regulated	(21)
LINC00152	476/475	13	up-regulated	(22)
RP11-37B2.1	1359/1534	9	no reactive	(23)
ENST00000429730	55/30	1	down-regulated	(24)
uc011ncc.1	55/30	1	down-regulated	(24)
ENST00000457582	55/30	1	up-regulated	(24)
chr2:192293450-192304436þ	55/30	1	up-regulated	(24)
AC079767.4	554/561	1	down-regulated	(25)
RP11-99H8.1	31/35	1	decrease	(16)
ENST00000507373	31/35	1	decrease	(16)
RP1-90G24.6	31/35	1	increase	(16)
TCONS_00024847	31/35	1	increase	(16)
lncRNA-CD244	-	1	up-regulated	(28)
LOC152742	48/44	1	up-regulated	(29)
Lnc-HNRNPU-1:7	20	1	up-regulated	(30)
CD27-AS1:16	20	1	up-regulated	(30)
lnc-ABT1-3:5	20	1	up-regulated	(30)
lnc-CCNT1-1:1	20	1	up-regulated	(30)

seq/gene	sample(patient/HC)	variation	Change of expression	ref
lnc-ARG2-3:1	20	1	down-regulated	**(30)**
lnc-HSPA4-5:1	20	1	down-regulated	**(30)**
T150805	42/25	1	up-regulated	**(31)**
ENST00000416708	42/25	1	up-regulated	**(31)**
T274995	42/25	1	up-regulated	**(31)**
NR_126366	42/25	1	down-regulated	**(31)**
uc.48+	42/25	1	down-regulated	**(31)**
NR_105053	42/25	1	down-regulated	**(31)**
CTD-2281E23.2	34/35	3	increase	**(16)**
RP11-382A18.1	34/35	4	increase	**(16)**
RP11-298J20.3	34/35	1	decrease	**(16)**
AC016683.6	34/35	12	decrease	**(16)**

4. Discussion

According to the World Health Organization (WHO), tuberculosis is one of the top ten diseases in the world that causes death **(36)**. People who are exposed to this bacterium are at risk for active tuberculosis as well as latent tuberculosis. Numerous studies have shown that environmental and genetic factors are involved in the involvement and development of infectious diseases, especially tuberculosis **(37-39)**. By examining the biomarkers, it is possible to help in the timely treatment of this disease **(5, 6)**.

Microorganisms have about 98% of genes non-coding sequences, of which a significant percentage are lncRNA sequences that play a role in regulating gene expression **(40, 41)**. In other studies, on lncRNA, SNGH5 is located on chromosome 16. Studies have been performed on two of them in pancreatic cancer and lung cancer, which have high expression in lncRNA in lung cancer patients and vice versa in patients with pancreatic cancer; this lncRNA has downregulation and has been introduced as a biomarker **(42, 43)**. LncRnaGAS5, which is located on chromosome number one. Many studies have been done on this lncRNA, for example, in people with CAD, who have down-regulated lncRNA, and can be a promising biomarker **(44)**. In another study, lncRnaGAS5 was measured in people with ovarian cancer and it found that it could be used as a therapeutic target or biomarker. Also, another survey of the same gene in people with NSCLC (non-small-cell lung cancer) in the early stages of the disease leads to early detection and diagnosis **(45, 46)**. Studies on lncRNA H19 have been linked to many diseases. In pancreatic cancer, the expression of this lncRNA was measured, which was found to be highly expressed in the PANC-1 cell line, and its suppression prevents metastasis, which is a good candidate for the treatment of this cancer **(47, 48)**. Increased expression of H19 has been shown in some tumors such as breast cancer and hepatocellular carcinoma (HCC). This lncRNA also reacts with many mi-RNAs and proteins **(49)**. Studies measuring the effect of kidney disease have shown that lncRNA is up-regulated in the disease, which is shown to reduce renal fibrosis by turning off the gene. Therefore, suppression of lncRNA is a cure factor for kidney diseases **(50)**. H19 can be used as a biomarker in various malignancies, such as pancreatic ductal adenocarcinoma (PDAC), which is often associated with up-regulation in this disease. H19 also reacts with miRNA to regulate inflammation, oxidative stress, and fibrosis **(47)**. Studies in lnc NEAT1 have shown that the expression level in the tissues and plasma of people with NSCLC is higher than in normal tissues. High expression is associated with vascular invasion, lymphatic metastasis, tumor metastasis, and age Be considered **(51)**. Increased expression of this lncRNA in patients with esophageal squamous cell carcinoma (ESCC) causes cell proliferation and invasion and migration of cancer cells, which in this disease is referred to as NEAT1 as an oncogene. lncRNA regulation applies to diseases and cancers such as Laryngeal squamous cell carcinoma, Colorectal cancer, Hepatocellular cancer, Breast cancer, Ovarian cancer, Prostate cancer, and Glioma, except in Acute promyelocytic leukemia, where NEAT1 expression is low **(51)**. BRE-AS1 is one of the lncRNAs that has been studied in people with bladder cancer (BC), and it has been found that we have reduced expression in people with this disease. Also, high expression of this lncRNA reduces cell proliferation and thus reduces cancer growth. The target of this lncRNA is the STAT3 signaling pathway, which suppresses its

phosphorylation **(52)**. In another study, this lncRNA in non-small cell lung cancer (NSCLC) patients had the same results. In this study, the NR4A3 gene was positively associated with lncRNA, and as a result, this lncRNA could have the potential for treatment in these two diseases **(53)**. In patients with glioblastoma, PCED1B-AS1 was evaluated. It found that its expression in normal tissue was lower than that of glioblastoma and that those with high expression of this lncRNA had a shorter lifespan and survival. PCED1B-AS1 is also closely related to tumor size. PCED1B-AS1 translates mRNA, and HIF-1α causes tumorigenesis and the Warburg effect. Thus, this lncRNA is considered an oncogene and a therapeutic target by HIF-1α effect **(54)**. The role of LINC00152 or cytoskeleton regulator RNA (CYTOR) in various types of cancer is being investigated, which has been shown to have a high expression in patients with peripheral tissue and blood in NSCLC cancer. This lncRNA is also considered a biomarker and oncogene of this disease. CYTOR is effective in the invasion, migration, growth, and proliferation of NSCLC cells **(55)**. The study by Yang Yu et al. showed that lncRNA was closely associated with various cancers and tumors (gastric cancer, hepatocellular carcinoma, colon cancer, gallbladder cancer, and renal cell carcinoma) and could accelerate these diseases. Therefore, suppressing or controlling it can prevent the progression of the disease, which is a type of therapeutic goal. It can also give suitable biomarkers and prognosis. LINC00152 has a significantly high expression in most of the mentioned cancers, which is a critical point (56). One study found that high expression of LINC01857 had a poor prognosis for breast cancer. Restricting it reduces cell invasion and cell migration. It was found that increased transcription in H3K27Ac and CREB1 by CREBBP is involved in regulating LINC01857 expression **(57)**. PAX8-AS1 polymorphisms (rs4848320 and rs6726151) increase the risk of infection and risk factors in children with acute lymphoblastic leukemia. Some SNPs reduce the risk of cervical cancer (58, 59). Studies have shown that PIK3CD-AS2 shortens patients' life and promotes lung adenocarcinoma (LUAD). It also reduces apoptosis and inhibits p53 by binding to YBX1 **(60)**. Studies have shown that lncRNAs affect the body's immunity against tuberculosis and can also be used as a biomarker for therapeutic targets against tuberculosis **(14, 17, 28)**. In this systematic review study, we analyzed 19 articles to analyze the relationship between lncRNA and tuberculosis, in which articles 59 lncRNA were validated by qRT-PCR, which we used with all specifications using the sites https://lncipedia.org, http://bioinfo.life.hust.edu.cn/lncRNASNP#!/, https://rnacentral.org are listed in Tables 2 and 3. Unfortunately, eight lncRNA profiles were not found in the specified databases. Almost all lncRNA except 5 had dysregulation, 29 of which had up-regulation and 25 down regulations. As a result, we can use this 54 lncRNA as diagnostic biomarkers.

5. Conclusion

In summary, in this systematic review study, it was found that there is an acceptable association between lncRNA and SNP with tuberculosis and *M. tuberculosis*. Therefore, it was found that these regulatory factors play an important role as diagnostic biomarkers and the development of new therapies. However, more studies are needed to discover new lncRNAs and their association with tuberculosis.

Acknowledgment

Declared none.

Conflict of Interest

All authors – none to declare.

Funding

None declared.

References

1. Gagneux S. Ecology and evolution of Mycobacterium tuberculosis. Nat Rev Microbiol. 2018;16(4):202-13. [DOI:10.1038/nrmicro.2018.8] [PMID]
2. Faksri K, Kaewprasert O, Ong RT, Suriyaphol P, Prammananan T, Teo YY, et al. Comparisons of whole-genome sequencing and phenotypic drug susceptibility testing for Mycobacterium tuberculosis causing MDR-TB and XDR-TB in Thailand. Int J Antimicrob Agents. 2019;54(2):109-16. [DOI:10.1016/j.ijantimicag.2019.04.004] [PMID]
3. Marimani M, Ahmad A, Duse A. The role of epigenetics, bacterial and host factors in progression of Mycobacterium tuberculosis infection. Tuberculosis. 2018;113:200-14. [DOI:10.1016/j.tube.2018.10.009] [PMID]
4. Owens NA, Young CC, Laurentius LB, De P, Chatterjee D, Porter MD. Detection of the tuberculosis biomarker mannose-capped

lipoarabinomannan in human serum: Impact of sample pretreatment with perchloric acid. Anal Chim Acta. 2019;1046:140-7. [DOI:10.1016/j.aca.2018.09.037] [PMID] [PMCID]

5. Norbis L, Alagna R, Tortoli E, Codecasa LR, Migliori GB, Cirillo DM. Challenges and perspectives in the diagnosis of extrapulmonary tuberculosis. Expert Rev Anti Infect Ther. 2014;12(5):633-47. [DOI:10.1586/14787210.2014.899900] [PMID]
6. Loo JFC, Kwok HC, Leung CCH, Wu SY, Law ILG, Cheung YK, et al. Sample-to-answer on molecular diagnosis of bacterial infection using integrated lab--on--a--disc. Biosens Bioelectron. 2017;93:212-9. [DOI:10.1016/j.bios.2016.09.001] [PMID]
7. Spizzo R, Almeida MI, Colombatti A, Calin GA. Long non-coding RNAs and cancer: a new frontier of translational research? Oncogene. 2012;31(43): 4577-87. [DOI:10.1038/onc.2011.621] [PMID] [PMCID]
8. St Laurent G, Wahlestedt C, Kapranov P. The Landscape of long noncoding RNA classification. Trends Genet. 2015;31(5):239-51. [DOI:10.1016/j.tig.2015.03.007] [PMID] [PMCID]
9. Chen LL. Linking Long Noncoding RNA Localization and Function. Trends Biochem Sci. 2016;41(9):761-72. [DOI:10.1016/j.tibs.2016.07.006] [DOI:10.1016/j.tibs.2016.07.003]
10. Ma L, Bajic VB, Zhang Z. On the classification of long non-coding RNAs. RNA Biol. 2013;10(6):925-33. [DOI:10.4161/rna.24604] [PMID] [PMCID]
11. Zur Bruegge J, Einspanier R, Sharbati S. A Long Journey Ahead: Long Non-coding RNAs in Bacterial Infections. Front Cell Infect Microbiol. 2017;7:95. [DOI:10.3389/fcimb.2017.00095] [PMID] [PMCID]
12. Zhang X, Guo J, Fan S, Li Y, Wei L, Yang X, et al. Screening and identification of six serum microRNAs as novel potential combination biomarkers for pulmonary tuberculosis diagnosis. PLoS One. 2013;8(12):e81076. [PMCID] [DOI:10.1371/journal.pone.0081076] [PMID]
13. Wu Q, Zhong H, Bai H, Liu T, Song J, Wen Y, et al. Clinical relevance of the lnc-HNF1B-3:1 genetic polymorphisms in Western Chinese tuberculosis patients. J Clin Lab Anal. 2020;34(3):e23076-e. [DOI:10.1002/jcla.23076] [PMID] [PMCID]
14. Chen Z-L, Wei L-L, Shi L-Y, Li M, Jiang T-T, Chen J, et al. Screening and identification of lncRNAs as potential biomarkers for pulmonary tuberculosis. Sci Rep. 2017;7(1):16751. [PMID] [PMCID] [DOI:10.1038/s41598-017-17146-y]
15. Bai H, Wu Q, Hu X, Wu T, Song J, Liu T, et al. Clinical significance of lnc-AC145676.2.1-6 and lnc-TGS1-1 and their variants in western Chinese tuberculosis patients. J Obstet Gynecol Cancer Res. 2019;84:8-14. [DOI:10.1016/j.ijid.2019.04.018] [PMID]
16. Fu Y, Gao K, Tao E, Li R, Yi Z. Aberrantly Expressed Long Non-Coding RNAs In CD8(+) T Cells Response to Active Tuberculosis. J Cell Biochem. 2017; 118(12):4275-84. [DOI:10.1002/jcb.26078] [PMID]
17. He J, Ou Q, Liu C, Shi L, Zhao C, Xu Y, et al. Differential expression of long non-coding RNAs in patients with tuberculosis infection. Tuberculosis. 2017;107:73-9. [DOI:10.1016/j.tube.2017.08.007] [PMID]
18. Huang S, Huang Z, Luo Q, Qing C. The Expression of lncRNA NEAT1 in Human Tuberculosis and Its Antituberculosis Effect. Biomed Res Int. 2018; 2018:9529072. [DOI:10.1155/2018/9529072] [PMID] [PMCID]
19. Yan H, Xu R, Zhang X, Wang Q, Pang J, Zhang X, et al. Identifying differentially expressed long non-coding RNAs in PBMCs in response to the infection of multidrug-resistant tuberculosis. Infect Drug Resist. 2018;11:945-59. [DOI:10.2147/IDR.S154255] [PMID] [PMCID]
20. Song J, Liu T, Zhao Z, Hu X, Wu Q, Peng W, et al. Genetic polymorphisms of long noncoding RNA RP11-37B2.1 associate with susceptibility of tuberculosis and adverse events of antituberculosis drugs in west China. J Clin Lab Anal. 2019;33(5):e22880. [DOI:10.1002/jcla.22880] [PMID] [PMCID]
21. Li M, Cui J, Niu W, Huang J, Feng T, Sun B, et al. Long non-coding PCED1B-AS1 regulates macrophage apoptosis and autophagy by sponging miR-155 in active tuberculosis. Biochem Biophys Res Commun. 2019;509(3):803-9. [DOI:10.1016/j.bbrc.2019.01.005] [PMID]
22. Li J, Wu L, Guo W, Chen J, Hu X, Wang M, et al. Clinical relevance of LINC00152 and its variants in western Chinese tuberculosis patients. Oncotarget. 2017;8(70):115456-68. [DOI:10.18632/oncotarget.23297] [PMID] [PMCID]
23. Song J, Liu T, Jiao L, Zhao Z, Hu X, Wu Q, et al. RIPK2 polymorphisms and susceptibility to tuberculosis in a Western Chinese Han population. Infect Genet Evol. 2019;75:103950. [DOI:10.1016/j.meegid.2019.103950] [PMID]
24. Yi Z, Li J, Gao K, Fu Y. Identifcation of differentially expressed long non-coding RNAs in CD4+ T cells response to latent tuberculosis infection. J Infect. 2014;69(6):558-68. [DOI:10.1016/j.jinf.2014.06.016] [PMID] [PMCID]

25. Zhao Z, Zhang M, Ying J, Hu X, Zhang J, Zhou Y, et al. Significance of genetic polymorphisms in long non-coding RNA AC079767.4 in tuberculosis susceptibility and clinical phenotype in Western Chinese Han population. Sci Rep. 2017;7(1):965. [DOI:10.1038/s41598-017-01163-y] [PMID] [PMCID]

26. Zhao Z, Peng W, Wu L, Ying B. Correlation between lncRNA AC079767.4 variants and liver injury from antituberculosis treatment in West China. J Infect Chemother. 2020;26(1):63-8. [DOI:10.1016/j.jiac.2019.07.003] [PMID]

27. Fu Y, Xu X, Xue J, Duan W, Yi Z. Deregulated lncRNAs in B cells from patients with active tuberculosis. PLoS One. 2017;12(1):e0170712. [DOI:10.1371/journal.pone.0170712] [PMID] [PMCID]

28. Wang Y, Zhong H, Xie X, Chen CY, Huang D, Shen L, et al. Long noncoding RNA derived from CD244 signaling epigenetically controls CD8+ T-cell immune responses in tuberculosis infection. Proc Natl Acad Sci U S A. 2015;112(29):E3883-92. [DOI:10.1073/pnas.1501662112] [PMID] [PMCID]

29. Wang L, Xie B, Zhang P, Ge Y, Wang Y, Zhang D. LOC152742 as a biomarker in the diagnosis of pulmonary tuberculosis infection. J Cell Biochem. 2019;120:8949-55. [DOI:10.1002/jcb.27452] [PMID]

30. Zhang X, Liang Z, Zhang Y, Dai K, Zhu M, Wang J, et al. Comprehensive analysis of long non-coding RNAs expression pattern in the pathogenesis of pulmonary tuberculosis. Genomics. 2020;112(2): 1970-7. [DOI:10.1016/j.ygeno.2019.11.009] [PMID]

31. Li ZB, Han YS, Wei LL, Shi LY, Yi WJ, Chen J, et al. Screening and identification of plasma lncRNAs uc.48+ and NR_105053 as potential novel biomarkers for cured pulmonary tuberculosis. Int J Infect Dis. 2020;92:141-50. [DOI:10.1016/j.ijid.2020.01.005] [PMID]

32. Lin PL, Flynn JL. CD8 T cells and Mycobacterium tuberculosis infection. Semin Immunopathol. 2015;37(3):239-49. [PMID] [PMCID] [DOI:10.1007/s00281-015-0490-8]

33. Jasenosky LD, Scriba TJ, Hanekom WA, Goldfeld AE. T cells and adaptive immunity to Mycobacterium tuberculosis in humans. Immunol Rev. 2015;264 (1):74-87. [DOI:10.1111/imr.12274] [PMID]

34. Yang X, Yang J, Wang J, Wen Q, Wang H, He J, et al. Microarray analysis of long noncoding RNA and mRNA expression profiles in human macrophages infected with Mycobacterium tuberculosis. Sci Rep. 2016;6:38963. [DOI:10.1038/srep38963] [PMID] [PMCID]

35. Yao Y, Jiang Q, Jiang L, Wu J, Zhang Q, Wang J, et al. Lnc-SGK1 induced by Helicobacter pylori infection and highsalt diet promote Th2 and Th17 differentiation in human gastric cancer by SGK1/Jun B signaling. Oncotarget. 2016;7(15): 20549-60. [DOI:10.18632/oncotarget.7823] [PMID] [PMCID]

36. who. Tuberculosis 2019 [Available from: https://www.who.int/health-topics/tuberculosis#tab=tab_1.

37. Abel L, El-Baghdadi J, Bousfiha AA, Casanova JL, Schurr E. Human genetics of tuberculosis: a long and winding road. Philos Trans R Soc Lond B Biol Sci. 2014;369(1645):20130428. [DOI:10.1098/rstb.2013.0428] [PMID] [PMCID]

38. Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in Development and Disease: Background, Mechanisms, and Therapeutic Approaches. Physiol Rev. 2016;96(4):1297-325. [DOI:10.1152/physrev.00041.2015] [PMID]

39. Wang P, Xu J, Wang Y, Cao X. An interferon-independent lncRNA promotes viral replication by modulating cellular metabolism. Science. 2017;358 (6366):1051-5. [DOI:10.1126/science.aao0409] [PMID]

40. Dinger ME, Amaral PP, Mercer TR, Pang KC, Bruce SJ, Gardiner BB, et al. Long noncoding RNAs in mouse embryonic stem cell pluripotency and differentiation. Genome Res. 2008;18(9):1433-45. [DOI:10.1101/gr.078378.108] [PMID] [PMCID]

41. Li CH, Chen Y. Targeting long non-coding RNAs in cancers: progress and prospects. Int J Biochem Cell Biol. 2013;45(8):1895-910. [DOI:10.1016/j.biocel.2013.05.030] [PMID]

42. Zhang B, Li C, Sun Z. Long non-coding RNA LINC00346, LINC00578, LINC00673, LINC00671, LINC00261, and SNHG9 are novel prognostic markers for pancreatic cancer. Am J Transl Res. 2018;10(8):2648-58.

43. Lin Y, Holden V, Dhilipkannah P, Deepak J, Todd NW, Jiang F. A Non-Coding RNA Landscape of Bronchial Epitheliums of Lung Cancer Patients. Biomedicines. 2020;8(4):88. [PMID] [PMCID] [DOI:10.3390/biomedicines8040088]

44. Yin Q, Wu A, Liu M. Plasma Long Non-Coding RNA (lncRNA) GAS5 is a New Biomarker for Coronary Artery Disease. Med Sci Monit. 2017;23:6042-8. [DOI:10.12659/MSM.907118] [PMID] [PMCID]

45. Li C, Lv Y, Shao C, Chen C, Zhang T, Wei Y, et al. Tumor-derived exosomal lncRNA GAS5 as a

biomarker for early-stage non-small-cell lung cancer diagnosis. J Cell Physiol. 2019;234(11): 20721-7. [DOI:10.1002/jcp.28678] [PMID]

46. Li J, Yang C, Li Y, Chen A, Li L, You Z. LncRNA GAS5 suppresses ovarian cancer by inducing inflammasome formation. Biosci Rep. 2018;38(2): BSR20171150. [DOI:10.1042/BSR20171150] [PMID] [PMCID]
47. Yoshimura H, Matsuda Y, Yamamoto M, Michishita M, Takahashi K, Sasaki N, et al. Reduced expression of the H19 long non-coding RNA inhibits pancreatic cancer metastasis. Lab Invest. 2018;98(6):814-24. [DOI:10.1038/s41374-018-0048-1] [PMID]
48. Wang J, Zhao L, Shang K, Liu F, Che J, Li H, et al. Long non-coding RNA H19, a novel therapeutic target for pancreatic cancer. Mol Med. 2020;26(1): 30. [DOI:10.1186/s10020-020-00156-4] [PMID] [PMCID]
49. Abbastabar M, Sarfi M, Golestani A, Khalili E. lncRNA involvement in hepatocellular carcinoma metastasis and prognosis. Excli j. 2018;17:900-13.
50. Xie H, Xue JD, Chao F, Jin YF, Fu Q. Long non-coding RNA-H19 antagonism protects against renal fibrosis. Oncotarget. 2016;7(32):51473-81. [DOI:10.18632/oncotarget.10444] [PMID] [PMCID]
51. Yu X, Li Z, Zheng H, Chan MT, Wu WK. NEAT1: A novel cancer-related long non-coding RNA. Cell Prolif. 2017;50(2):e12329. [DOI:10.1111/cpr.12329] [PMID] [PMCID]
52. Zhang L, Liu B, Deng QH, Li JX. LncRNA BRE-AS1 acts as a tumor suppressor factor in bladder cancer via mediating STAT3. Eur Rev Med Pharmacol Sci. 2020;24(10):5320-8.
53. Zhang M, Wu J, Zhong W, Zhao Z, Liu Z. Long non-coding RNA BRE-AS1 represses non-small cell lung cancer cell growth and survival via up-regulating NR4A3. Arch Biochem Biophys. 2018;660:53-63. [DOI:10.1016/j.abb.2018.09.013] [PMID]
54. Yao Z, Zhang Q, Guo F, Guo S, Yang B, Liu B, et al. Long Noncoding RNA PCED1B-AS1 Promotes the Warburg Effect and Tumorigenesis by Upregulating HIF-1α in Glioblastoma. Cell Transplant. 2020;29: 963689720906777. [PMID] [PMCID] [DOI:10.1177/0963689720906777]
55. Yu H, Li SB. Role of LINC00152 in non-small cell lung cancer. J Zhejiang Univ Sci B. 2020;21(3):179-91. [DOI:10.1631/jzus.B1900312] [PMID] [PMCID]
56. Yu Y, Yang J, Li Q, Xu B, Lian Y, Miao L. LINC00152: A pivotal oncogenic long non-coding RNA in human cancers. Cell Prolif. 2017;50(4):e12349. [DOI:10.1111/cpr.12349] [PMID] [PMCID]
57. Xiong Y, Gu Y, Wang F, Li L, Zhu M, Wang N, et al. LINC01857 as an oncogene regulates CREB1 activation by interacting with CREBBP in breast cancer. J Cell Physiol. 2019;234(8):14031-9. [DOI:10.1002/jcp.28090] [PMID]
58. Han J, Zhou W, Jia M, Wen J, Jiang J, Shi J, et al. Expression quantitative trait loci in long non-coding RNA PAX8-AS1 are associated with decreased risk of cervical cancer. Mol Genet Genomics. 2016;291(4):1743-8. [DOI:10.1007/s00438-016-1217-9] [PMID]
59. Bahari G, Hashemi M, Naderi M, Sadeghi-Bojd S, Taheri M. Long non-coding RNA PAX8-AS1 polymorphisms increase the risk of childhood acute lymphoblastic leukemia. Biomed Rep. 2018; 8(2):184-90. [DOI:10.3892/br.2017.1028] [PMID] [PMCID]
60. Zheng X, Zhang J, Fang T, Wang X, Wang S, Ma Z, et al. The long non-coding RNA PIK3CD-AS2 promotes lung adenocarcinoma progression via YBX1-mediated suppression of p53 pathway. Oncogenesis. 2020;9(3):34. [PMID] [PMCID] [DOI:10.1038/s41389-020-0217-0]