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Review Article

Long non-coding RNA transcripts in *Mycobacterium tuberculosis*-host interactions

Mahalakshmi Vijayaraghavan [a], Shrikanth S. Gadad [a,c,d,*], Subramanian Dhandayuthapani [b,c,**]

[a] Center of Emphasis in Cancer, Department of Molecular and Translational Medicine, Texas Tech University Health Sciences Center El Paso, Texas-79905, USA
[b] Center of Emphasis in Infectious Diseases, Department of Molecular and Translational Medicine, Texas Tech University Health Sciences Center El Paso, Texas-79905, USA
[c] Frederick L. Francis Graduate School of Biomedical Sciences, Texas Tech University Health Sciences Center El Paso, Texas-79905, USA
[d] Mays Cancer Center, UT Health San Antonio MD Anderson Cancer Center, San Antonio, TX 78229, USA

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ABSTRACT

Tuberculosis (TB) persists as a significant health threat, affecting millions of people all over the world. Despite years of control measures, the elimination of TB has become a difficult task as morbidity and mortality rates remain unaffected for several years. Developing new diagnostics and therapeutics is paramount to keeping TB under control. However, it largely depends upon understanding the pathogenic mechanisms of *Mycobacterium tuberculosis* (Mtb), the causative agent of TB. Mtb is an intracellular pathogen capable of subverting the defensive functions of the immune cells, and it can survive and multiply within humans' mononuclear phagocytes. Emerging evidence indicates that long non-coding RNAs (lncRNAs), a class of RNA molecules with limited coding potential, are critical players in this intricate game as they regulate gene expression at transcriptional and post-transcriptional levels and also by chromatin modification. Moreover, they have been shown to regulate cellular processes by controlling the function of other molecules, such as DNA, RNA, and protein, through binding with them. Recent studies have shown that lncRNAs are differentially regulated in the tissues of TB patients and cells infected in vitro with Mtb. Some dysregulated lncRNAs are associated with essential roles in modulating immune response, apoptosis, and autophagy in the host cells, adding a new dimension to TB pathogenesis. In this article, we provide a comprehensive review of the recent literature in this field and the impact of lncRNAs in unraveling pathogenic mechanisms in TB. We also discuss how the studies involving lncRNAs provide insight into TB pathogenesis, especially Mtb-host interactions.

1. Introduction

Tuberculosis (TB) is one of the prominent chronic respiratory diseases caused by an intracellular pathogen called *Mycobacterium tuberculosis* (Mtb). Although TB has been affecting humans for thousands of years, it gained attention when the World Health Organization (WHO) declared TB a global public health emergency following an epidemic in the early years of the nineties [1]. Moreover, despite years of TB control and surveillance programs, TB remains one of the deadliest diseases caused by a pathogen. According to a recent report by the WHO, globally, TB made about 10 million people sick and killed about 1.3 million people in the year 2022, in addition to latently infecting millions of individuals [2]. Currently, one-quarter of the world population is estimated to have latent TB infection (LTBI), and these individuals, although they harbor live bacilli, remain non-symptomatic and non-contagious [3]. However, five percent of LTBI individuals are at risk of developing TB during their lifetime. A potential danger is Mtb–HIV co-infection, which can accelerate the disease processes reciprocally, leading to the death of the infected individuals [2]. In areas where both TB and HIV are endemic, the LTBIs, due to their large numbers, are at

* Corresponding author. Center of Emphasis in Cancer, Department of Molecular and Translational Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, 130 Rick Francis St. El Paso, Texas, 79905, USA.
** Corresponding author. Center of Emphasis in Infectious Diseases, Department of Molecular and Translational Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, 130 Rick Francis St. El Paso, Texas, 79905, USA.
E-mail addresses: shrikanth.gadad@ttuhsc.edu (S.S. Gadad), s.dhandayuthapani@ttuhsc.edu (S. Dhandayuthapani).

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higher risk of acquiring HIV infection than the TB patients. The emergence of Multi-drug Resistant TB (MDR-TB) and Extensively Drug Resistant TB (XDR-TB) is also of significant concern. Notably, treatment of TB caused by XDR strains is more challenging than before because it is resistant to both first-line anti-TB drugs (rifampicin and isoniazid), fluoroquinolone (FQ), and any of the second-line injectable drugs such as capreomycin, kanamycin or amikacin [4–6]. Thus, identifying novel diagnostic markers and developing host-directed therapies (HDT) is central to the timely treatment of TB cases, which in turn requires an understanding of the Mtb-host interplay at the molecular level.

Recent studies have explored Mtb-host interaction through gene expression analysis using techniques such as RNA-seq, which revealed differential expression of genes (DEG) in the host tissues [7–13]. The DEGs included non-protein coding genes, also called non-coding RNAs (ncRNAs), which comprise 97 % of the human genome [14]. Although the non-coding RNAs comprise several types, long non-coding RNAs (lncRNAs) are the most abundantly expressed ncRNAs in these tissues, indicating their critical roles in the pathogenic process of TB. Similar to Mtb, differential expression of lncRNA genes has also been noticed in other bacterial and viral infections, and they seem to be regulating the pathogenic processes, particularly the immune responses [15–17]. Furthermore, lncRNAs are emerging as important regulators of epigenetic, transcriptional, post-transcriptional, translational, and post-translational mechanisms [18]. Other additional lncRNA functions involve cell cycle regulation, structural integrity, imprinting, reprogramming, stem cell pluripotency, apoptosis, etc. [19]. In this article, we review and discuss the recent developments on lncRNAs in the TB field, particularly the roles of lncRNAs in pathogenesis and host-pathogen interactions. Our review differs from other recent reviews in this field [20–25] as it focuses more on the features of lncRNAs that have definite roles in the pathogenesis or host-pathogen interactions.

2. Long non-coding RNAs (lncRNAs), their types and functions

LncRNAs are autonomously transcribed RNAs that are longer than 200 nucleotides and have an optimal cut-off size in the biochemical and biophysical RNA purification process by suppressing most canonical RNAs, such as 5S Ribosomal RNAs (5SrRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs), as well as microRNAs (miRNAs), small interfering RNAs (siRNAs), and Piwi interacting RNAs (piRNAs) [26]. Though lncRNAs have no coding potential, they appear to have characteristics similar to protein-coding genes, including 5′-capping, RNA polymerase II transcription, alternative RNA splicing, and poly-adenylation. Additionally, their regulatory roles in influencing an active or inactive phase of gene expression are attained by interactions with transcription factors (TF) or chromatin-modifying proteins/readers or with their specific protein-binding motifs like interaction with RNA-binding proteins (RBP). Also, they explicitly attach to the DNA strands to form an RNA–DNA triplex structure to block the transcription [18,27].

The classification of lncRNAs seems empirical [28] and is often based on their genome position, such as intronic, intergenic, sense, anti-sense, and bidirectional. LncRNAs transcribed entirely from within the introns of protein-coding genes are designated as intronic lncRNAs, and they appear to regulate the expression of their corresponding host genes in eukaryotes [29]. Several lncRNAs overlap other genes and can either be in the sense or anti-sense direction to those other genes. Anti-sense lncRNAs or natural antisense transcripts (NAT) are intrinsically transcribed from the antisense strand of protein-coding genes. In addition, they are the most abundant type of lncRNAs found in the mouse and human genome. NATs are further sorted into *cis*-NATs and *trans*-NATs. *cis*-NATs complement its overlapping protein-coding DNA sequence, while *trans*-NATs are situated in distinctive positions of the genome and are the complement of protein-coding DNA sequence. Sense lncRNAs are located within other genes containing exons but in the sense direction. Intriguingly, few sense lncRNAs can perform as both protein-coding genes and RNA function. For example, besides translating into protein, steroid receptor RNA activator (SRA) gene transcript can also function as a scaffold for co-activators and repressors to form complexes regulating transcription [28]. Among these, long-intergenic non-coding RNAs (lincRNAs) are the most abundant and widely studied lncRNAs located and transcribed from different intergenic regions and are >1 kb away from neighboring genes. So far, >8000 human lincRNAs have been identified, and now they are considered the largest subclass of lncRNA in the human genome [30]. The final group of lncRNA genes, which are located head-to-head within 1 kb of protein-coding genes in the genome but in the opposite direction, are bi-directional lncRNAs.

Further, based on their intracellular distribution, lncRNAs are classified as nuclear lncRNAs and cytoplasmic lncRNAs. Nuclear lncRNAs regulate the expression of proximal or distal genes by recruiting chromatin remodeler complexes. In contrast, cytoplasmic lncRNAs impede the stability and translation of mRNA and transduce extracellular signaling by operating as protein scaffolds, RBP decoys, antisense RNA or miRNA sponges [18]. Moreover, lncRNAs can also act through specific base-pairing with other RNA subtypes, such as microRNAs (miRNAs). Thus, the regulation of cellular processes by lncRNAs partly hinders the functions of miRNAs. Although the functions of some lncRNAs in cellular homeostasis and disease states have been established, many lncRNAs remain uncharacterized and are yet to be analyzed in detail [21,29,31].

3. Pathogenesis of TB

It appears that TB patients who spread Mtb bacilli through coughing, sneezing, and speech are the significant sources of Mtb transmission. The bacilli released in the air become aerosol droplets and enter the healthy human body through inhalation (reviewed in Ref. [32]). When they reach the alveolar space of the lungs, they will be phagocytosed by the alveolar macrophages. It is assumed that specific interactions between the surface ligands of the bacilli or pathogen-associated molecular patterns (PAMPs) and the pattern recognition receptors (PRRs) of macrophages allow the entry of the bacilli into the cells [33]. Bacilli also seem to enter the phagocytes non-specifically through opsonization [33]. Regardless, the endosomes carrying the phagocytosed bacilli mature into early phagosomes, as do endosomes carrying any other pathogens. However, unlike others, the phagosomes with Mtb bacilli fail to mature further and fuse with lysosomes to lyse or digest the engulfed bacteria [34–37]. It has been reported that Mtb prevents the phagosome maturation and subsequent acidification of the phagosomal compartment through its virulent surface components and by releasing effector molecules into the phagosomal compartment [38–41]. This ability to prevent phagosomal maturation or the ‘phagosomal maturation arrest’ by Mtb is considered a unique strategy to escape from the lytic activity of the lysosomes. Intriguingly, Mtb also has mechanisms to escape from the phagosomes to the cytosol of the macrophages [42]. Thus, it has been speculated that Mtb modulates the hostile macrophages as its niche to survive, replicate, and spread the bacteria to the surrounding cells and tissues [43,44]. However, the infected macrophages induce proinflammatory responses, particularly IFN-γ, that recruit additional monocytes and macrophages to contain the infection by forming granulomas [45,46]. Simultaneously, some of the Mtb-infected macrophages and other antigen-presenting cells, like dendritic cells, migrate to the local lymph nodes and present Mtb antigens through MHC pathways to induce adaptive immune responses [47,48]. Immune cells, mainly activated $CD4^+$ T cells, are recruited to the site of Mtb replication, and these cells, through their Th1 response, either eliminate or ‘contain’ the infection [49,50]. In addition to $CD4^+$ T cells, $CD8^+$ T cells also play a role in this process [51]. However, failure of elimination or containment allows the bacteria to multiply and disseminate, leading to primary TB disease [52]. Mtb survives within the granulomas in a latent or dormant stage for an indefinite period or until the immune mechanism weakens for some reason [53]. This stage is known as latent TB infection or LTBI.

Table 1
LncRNA expression and its relative function with mycobacterial infection.

LncRNA	Expression	Sample Type/Infection	Function	Reference
COX2	Up	Plasma of TB patients THP-1 macrophages infected with Mtb RAW264.7 macrophages infected with BCG	Inflammatory responses Apoptosis	Li et al., 2020 Xu et al., 2020
PACER (COX2)	Up	Human MDMs infected with Mtb HN878 PBMC from TB patients THP-1 macrophages infected with Mtb	Inflammatory responses Immune response	Tamgue O et al., 2021 Huang et al., 2018
NEAT1	Up	Peripheral blood and granulomatous tissues from Spinal TB patients and THP-1 cells infected with Mtb	Immune response IL-6	Zheng J et al., 2022
CD244	Up	$CD8^+$ T-cells from TB patients	Epigenetic regulation	Wang Y et al., 2015
NORAD	Up	Serum of Pulmonary tuberculosis (PTB) patients. THP1 & RAW264.7 macrophages infected with Mtb H37Rv	Inflammatory mediator	Sun W et al., 2022
MIAT	Up	THP-1 macrophages infected with BCG	Promotes apoptosis and autophagy	Jiang F et al., 2021
DANCR	Up	PBMCs from Pulmonary TB patients	Promotes autophagy pathway	Qu Y et al., 2023
MEG3	Up Down	THP-1 cells infected with *M. smegmatis* THP-1 derived macrophages infected with BCG	TGFβ signaling Autophagy pathway	Sharbati S et al., 2019 Pawar K et al., 2016
NR 003508	Up	RAW264.7 macrophages infected with BCG	Promotes programmed necrosis via sponging miR-346-3p to regulate RIPK1	Liu L et al., 2023
XIST	Up	RAW264.7 macrophages, hMDM and dendritic cells	NF-κB signaling via miR-125b-5p	Luo XB et al., 2022
LncRNA-SNHG16	Up	Serum from TB patients and THP-1 cells infected with Mtb	Positive correlation with TNF-α, IL-6 and IL-1β	Sun et al., 2022
LINC00870	Up	PBMCs from TB patients	Activates JAK/STAT pathway	Jianfang W et al., 2022
XLOC_012582	Up	B cells from TB patients	TLR and TGFβ signaling	Fu Y et al., 2017 a
LincRNA XLOC_014219	Up	$CD8^+$ T cells from TB patients	Dysfunction of $CD8^+$ T cells	Fu Y et al., 2017 b
LNC13	Up	Whole blood of active TB patients	Immune response	Kameni et al., 2022
LincRNA-p21	Up	MDMs infected with Mtb HN878	Immune response suppresses IL-6	Tamgue et al., 2021
CGB	Down	LncRNA CGB-KO mice with TB infection and lymphocytes from Mtb-infected mice/patients	Anti-TB immunity/Histone methylation	Yang et al., 2022
TGS-1	Down	Whole blood of TB patients	TLR Signaling	Bai H et al., 2019
PCED1B-AS1	Down	$CD14^+$ monocytes from Tb patients	Autophagy pathway	Li M et al., 2019
EPS	Down	RAW264.7 macrophages infected with BCG	Apoptosis and autophagy regulation via JNK/MAPK signaling pathway	Ke Z et al., 2020
Lnc-EST12	Down	RAW264.7 macrophages and mouse macrophages	JAK2-STAT5a signaling pathway	Yao Q et al., 2022
GAS5	Down	Serum samples of TB patients THP-1 macrophages infected with Mtb	Pro-inflammatory cytokines	Li et al., 2022
LINCMIR99AHG	Down	BMDM/hMDMs infected with Mtb HN878 Mice infected with Mtb HN878	Role in Mtb survival within the host	Gcanaga et al., 2022

When a favorable situation arises, the latent Mtb gets reactivated, multiplies and disseminates, and causes secondary or reactivation TB [54]. Although several of these processes are not fully understood, Mtb interacts with host cells at all infection stages, affecting gene expression in both the host and Mtb.

4. LncRNAs and pathogenesis of tuberculosis

It is well known that pathogenic microbes regulate cellular processes in the host cells for their survival and replication, including the immune pathways related to innate and adaptive immunity [15,17]. This regulation is partly achieved by altering or differentially regulating the expression of lncRNAs in the host cells [16,20–23,55]. In TB, several lncRNAs are differentially expressed, impacting the host's immune response. Initial studies identified the differential expression of 1113 lncRNAs in $CD4^+$ T cells from active TB patients and 449 lncRNAs in individuals with latent TB infection (LTBI) compared to healthy controls [56]. Further investigations have shown differential lncRNA expression across various cell types and bodily fluids of TB patients, including PBMCs, monocytes, plasma, serum, T cells, B cells, and macrophages infected in vitro with virulent and avirulent strains of Mtb or other mycobacteria [57–68]. As summarized in (Table 1), many of the differentially expressed lncRNAs show a strong association with the regulation of immune response, both innate and adaptive (Fig. 1). Further, some lncRNAs in TB patients reveal single nucleotide polymorphisms (SNPs) (Table 2) that impact TB susceptibility or disease progression (Fig. 2). In the following section, we discuss specific lnRNAs that have been well-characterized in TB pathogenesis including *HOTAIR*, *LincRNA-COX2*, *NEAT1*, *PCED1B-AS1*, *LncRNA-CD244*, *NORAD*, *MIAT*, *DANCR*, *MEG*, *XIST*, and others, as well as their roles in host-pathogen interactions.

4.1. LincRNA cyclooxygenase 2 (LincRNA-COX2)

Cyclooxygenase-2 (*COX2*) is encoded by a gene situated on chromosome 1 at the q31 position, and it plays a vital role in inflammation [69]. In contrast, *lincRNA-COX2* is situated at 1q25 and is induced by LPS, regulating inflammatory immune response in macrophages through TLR signaling (TLR-4) [70]. Notably, *lincRNA-COX2* is approximately 51 kb upstream of the protein-coding cyclooxygenase-2 (*COX2*) gene, highlighting its significance in *COX2* regulation [70,71]. Cellular characterization further revealed that it is highly expressed in the lungs, particularly in alveolar macrophages, in response to LPS [72]. In TB patients, the levels of *lincRNA-COX2* were noticed to be elevated in the plasma, which was accompanied by upregulation of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6)

and interferon-γ (IFN-γ) [73]. This study also noted elevated *lincRNA-COX2* and iNOS levels in the mononuclear cells of TB patients. Since TB is primarily a lung disease, higher levels of lung-related *lincRNA-COX2* in the plasma might indicate its possible leakage from the lungs. In fact, *lincRNA-COX2* influences inflammation through the NF-kB signaling pathway in macrophages [70]. Experimental studies have verified that infection of macrophages with avirulent (H37Ra) Mtb strain increased the expression of both *lincRNA-COX2* and NF-kB and si-RNA mediated *lincRNA-COX2* knockdown decreased the levels of NF-kB [73], demonstrating the link between these two molecules. Similar to Mtb, infection of macrophages by BCG also upregulated the expression of *lincRNA-COX2*, which was accompanied by increased apoptosis [71]. In addition, TLR-2 signaling also activated the expression of *lincRNA-COX2*, and its knockdown provoked apoptosis-associated genes and increased ROS and ER stress levels in macrophages [74]. Further, consistent with its proinflammatory nature, the knockdown of *lincRNA-COX2* in macrophages suppressed the elimination of intracellular BCG, which was ascribed to the inhibition of M1 polarization and production of nitric oxide (NO) due to the absence of *lincRNA-COX2* [71]. Moreover, *PACER* lncRNA (also known as *lincRNA-COX2*), a positive regulator of its proximal pro-inflammatory gene Ptgs-2, was found to be upregulated in monocyte-derived macrophages (MDMs) upon infection with the hypervirulent clinical Mtb HN878 strain [75]. These observations strongly indicate that *lincRNA-COX2* is an essential regulator of inflammatory responses during Mtb infection.

4.2. Nuclear paraspeckle assembly transcript 1 (NEAT1)

An abundant lncRNA in the nucleus of mammalian cells, *NEAT1* can generate large gigantic ribonucleoproteins (RNPs) inside the nucleus by interacting with specific RNA-binding proteins [76]. It has two isoforms termed *NEAT1_1* and *NEAT1_2*, but the latter is critical for assembling RNPs or paraspeckles [77]. It regulates innate immune response and inflammation, particularly inflammasome activation in macrophages [78]. It was also abnormally upregulated in somatic malignant colorectal cancer tumor growth [79]. The dominant expression of *NEAT1*, *NEAT1_1,* and *NEAT1_2* was also found in Mtb-infected THP-1 cells [80] and peripheral blood mononuclear cells (PBMCs) of active and granulomatous spinal TB patients [81]. In TB patients, NEAT1 expression is associated with the increased expression of IL-6 and increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [80,81]. Further, a functional study noted that *NEAT1* activates inflammasomes in mouse macrophages [78], and its silencing decreased Mtb clearance [80]. Similarly, the depletion of *NEAT1_1* and its isoform *NEAT1_2* in HeLa cells increased susceptibility to *Salmonella* infection [82], indicating that *NEAT1*-mediated immune response is related to anti-bacterial activity.

4.3. LncRNA-cluster of differentiation 244 (lncRNA-CD244)

CD244 is a transmembrane signaling receptor from the immunoglobulin superfamily located on chromosome 1q23.3. While CD244-mediated signaling has been shown to upregulate the production of *lncRNA-CD244* located at chromosome 22, *lncRNA-CD244* itself plays a critical role in immune suppression by inhibiting IFN-γ and TNF-α levels [83,84]. It is also essential for modulating immune responses through cytokine signaling pathways in various immune cells, including monocytes, natural killer (NK) cells, $CD8^+$ T cells, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs) [84,85]. Intriguingly, the levels of CD244 were upregulated in $CD8^+$ T cells of TB patients, and this upregulation was associated with the enhanced expression of the *lncRNA-CD244* and reduced expression of INF-γ and TNF-α, compared to healthy controls [84]. On the other hand, the knockdown of *lncRNA-CD244* expression reversed the expression of INF-γ and TNF-α to normal levels. It was assumed that *lncRNA-CD244* inhibits the expression of INF-γ and TNF-α by methylating ifng/tnfa loci using the enhancer of zest homolog 2 (EZH2) that methylates H3K27me1 and H37K27me3 [84]. This is supported by the physical association of *lncRNA-CD244* with the EZH2 in $CD8^+$ T cells. Further, it was observed that the adoptive transfer of $CD8^+$ T cells repressed for the *lncRNA-CD244* expression to mice infected with Mtb showed relatively lower bacterial load and pathological changes than the control mice [84]. It appears, therefore, that Mtb purposely upregulates CD244 through *lncRNA-CD244* through CD244 signaling in $CD8^+$ T cells to evade the proinflammatory immune response of INF-γ and TNF-γ, suggesting that upregulation of *lncRNA-CD244* may be one of the survival strategies of Mtb.

4.4. Noncoding RNA activated by DNA damage (NORAD)

NORAD or *LINC00657* is located on chromosome 20q11.23 and is known for regulating inflammation in cerebral ischemia-reperfusion injury through miR-30a-5p/YwHAG [86]. Its upregulation has been noticed in lung cancer tissues [87] and in patients with sepsis [88]. Serum samples of pulmonary tuberculosis (PTB) patients also showed significantly higher levels of *NORAD* than healthy controls, which correlated with elevated levels of inflammatory cytokines such as IL-1 β, TNF-α, and IL-6 [89]. In addition, Mtb infection increased *NORAD* levels in THP-1 and RAW264.7 macrophages, increasing inflammation and macrophage viability [89]. *NORAD* appears to achieve this by negatively regulating miR-618 because elevated miRNA levels suppress macrophage inflammation and viability. The remarkably elevated *NORAD* levels in PTB patients may suggest that it is a potential diagnostic marker for PTB.

4.5. LncRNA myocardial infarction-associated transcript (MIAT)

MIAT plays a crucial role in disease pathogenicity, particularly in cancer and vascular and neurological disorders [90]. It also facilitates cellular functions such as proliferation, apoptosis, and invasion in various diseases [90]. Additionally, there is evidence that *MIAT* has a role in activating inflammatory response [91]. One study observed a time-dependent increase in *MIAT* expression in BCG-infected THP-1 macrophages, which decreased autophagy-associated proteins LC3-II and Beclin-1 and increased p62 levels, leading to the inhibition of the autophagy process during BCG infection [92]. There is speculation that *MIAT* acts as an endogenous sponge of miR-655 and negatively regulates its expression, impacting downstream targets such as ULK1, an essential autophagosome protein [92]. By competitively binding to miR-655, *MIAT* modulates ULK1 expression, further influencing macrophage apoptosis and autophagy through miR-655/ULK1 axis [92]. Modulation of *MIAT* and prevention of autophagy by BCG may be an important pathogenic mechanism for its survival inside the host cells. At this point, it is unclear whether Mtb modulates *MIAT* expression in the host cells, although the possibility exists.

4.6. LncRNA-differentiation antagonizing non-protein coding RNA (DANCR)

In cancer, the aberrant expression of *DANCR* has been linked to tumor progression by promoting cell proliferation, invasion, and migration while also suppressing apoptosis [93]. The expression of *DANCR* was found to be elevated in the peripheral blood mononuclear cells (PBMCs) of pulmonary tuberculosis and THP-1 cells infected with H37Ra [94]. Further investigations into *DANCR*'s role in TB uncovered its involvement in autophagosome formation by elevating the expression of molecules such as STAT3, RHEB, ATG4D, ATG5, and LC3 by sponging miR1301-3p and miR5194 [94]. Consistent with this, overexpression of *DANCR* in macrophages led to more efficient elimination of avirulent Mtb H37Ra infection, indicating its role in antibacterial activity [94]. Current strategies to develop host-directed therapy for TB include autophagy as one of the mechanisms to clear bacterial burden [95], and it has recently been reported that coadministration of

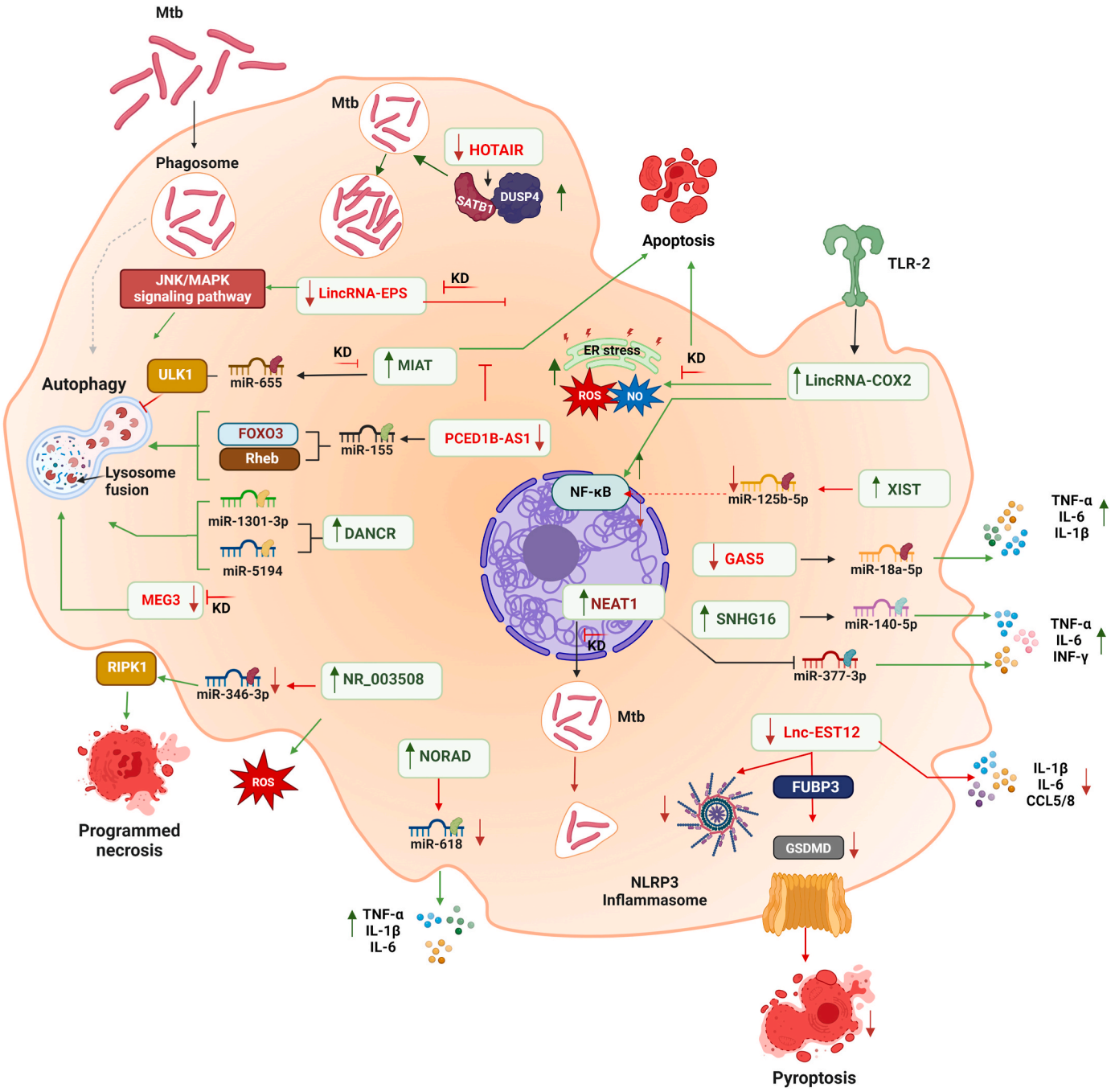

Fig. 1. Schematic showing the *M. tuberculosis*-infected cells/tissues used to determine the lncRNA expression by different studies. LncRNAs shown in green and red font are Up- and down-regulated, respectively.

rapamycin, an autophagy inducer, with clofazimine resulted in an enhanced bacterial reduction in mouse studies [96]. Thus, the observation that overexpression of *DANCR* could eliminate intracellular Mtb qualifies it as a potential candidate for targeting anti-TB therapy.

4.7. LncRNA maternally expressed gene 3 (MEG3)

MEG3, located in chromosome 14q32, stands out for its tumor-suppressive properties [97]. Its downregulation in bladder cancer triggers autophagy and fuels cell proliferation, while its overexpression in hepatocellular and cervical cancer diminishes autophagy [98]. Concerning mycobacterial infections, *MEG3* reveals an intricate pattern of expression. In macrophages, it was upregulated by the infection of non-pathogenic *M. smegmatis* but unaffected and down-regulated by pathogenic *M. avium* subsp *hominissuis* and *M. bovis* BCG, respectively [97,99]. This is striking because *M. avium* and BCG have the ability to survive in the intracellular environment in contrast to avirulent *M. smegmatis*. However, it has been reported that *M. smegmatis* down-regulates *MEG3* through methylation of its promoter region by DNA methyl transferases DNMT1 and DNMT3b, which results in the inhibition of TGF-β expression [21]. The inhibition of TGF-β is expected to allow the killing and processing of *M. smegmatis* but not the pathogenic *M. avium* [99]. In contrast, the down-regulation of *MEG3* by *M. bovis* BCG seems to induce autophagy in macrophages. Knockdown of *MEG3* in macrophages increased autophagy and enhanced clearance of BCG, possibly indicating that down-regulation of *MEG3* does not favor

Table 2
Single nucleotide polymorphisms (SNPs) in lncRNA and their role in TB risk or disease processes.

LncRNA	SNPs analyzed	Patients/populations	Disease Outcome	Reference
NEAT1	rs223895, rs3741384, rs3825071, rs5122715	Chinese population with pulmonary tuberculosis (PTB)	No significant associations between SNPs and risk for PTB	Li et al., 2022
HOTAIR	rs12427129, rs1899663, rs4759314, rs7958904	Pulmonary tuberculosis patients (PTB)	No significant associations between SNPs and susceptibility to PTB	Wang et al., 2023
THRIL	rs1055472 and rs11058000	Pulmonary tuberculosis patients (PTB)	No significant associations between SNPs and susceptibility to PTB.	Wang et al., 2023
AC007128.1	rs12333784, rs6463794, rs720964	Chinese Han population	SNP rs12333784 is associated with increased susceptibility to PTB.	Yan et al., 2021
AC079767.4	rs12477677 rs10178277, rs1055228, and rs1055229	Western Chinese Han TB population	rs12477677 is associated with decreased susceptibility to TB.	Zhao et al., 2017
HNF1B-3:1	rs2542670, rs1051838, rs1416, rs4262994, rs12939622, rs8075185, rs2688	Western Chinese PTB and EBTB patient	rs12939622 and rs4262994 are associated with an increased risk of fever rs2542670 is associated with thrombocytopenia, leukopenia, and chronic kidney damage following drug administration.	Wu et al., 2019
CASC8	rs7836840 rs7825118, rs9297758, and rs69814244 SNPs	Chinese Han TB patients	rs7836840 is associated with an increased risk of TB rs7825118 and rs9297758 are associated with lower Hb concentrations rs69814244 is associated with higher levels of ALT (alanine aminotransferase).	Liu et al., 2019
lncRNA-TGS1-1	rs4737420	West China Hospital	rs4737420 is associated with a decreased risk of leukopenia	Bai et al., 2018
lnc-AC145676.2.1-6	rs111352767	West China Hospital	No risk association	Bai et al., 2018

the survival of BCG within the intracellular environment. However, it may be assumed that BCG's efficacy as a vaccine may partly be due to the processing of its antigen through the autophagic pathway by the down-regulation of *MEG3*. A previous study showing that a recombinant BCG capable of inducing autophagy is more immunogenic and efficacious than BCG supports this view [100]. Surprisingly, whether Mtb infection manipulates the *MEG3* expression in macrophages is unknown. A recent study has reported that *MEG3* could be induced by lipopolysaccharides (LPS) through the TLR-4 pathway in kidney epithelial cells [101]. Although Gram-positive mycobacteria do not possess LPS on their surface, they have some surface glycoproteins [102] and heat shock proteins [103] that interact with TLR-4. Nevertheless, whether mycobacteria use TLR-4 signaling to regulate *MEG3* remains to be explored.

4.8. LncRNA NR_003508

This lncRNA has been reportedly involved in LPS-induced acute respiratory syndrome [104]. Mouse RAW264.7 macrophages infected with BCG had elevated expression of this lncRNA [105]. Simultaneously, these cells showed increased cell death due to programmed necrosis, inhibited by siRNA to lncRNA *NR_003508* [105], suggesting a link between the lncRNA and BCG-induced cell death. Further studies revealed that this lncRNA acted as a competing endogenous RNA (ceRNA) to mir-346-3p, which regulates the expression of necrosis-related protein RIPK1 [105]. Induction of necrosis in the host cells by Mtb is an essential pathogenic mechanism for its dissemination [105], and it appears that lncRNA *NR_003508* positively regulates this cellular process in Mtb-infected cells. This lncRNA is one of the promising targets for developing Host-directed therapies against TB.

4.9. X-inactive -specific transcript (XIST)

XIST silences X-chromosome transcription through a cascade of events, primarily by modifying the histones [106]. It interacts with SHARP/SPEN proteins to recruit histone deacetylase HDAC3 and with polycomb repressive complex 1 (PRC1) to ubiquitinate histone H2A [107–109]. Expression of *XIST* is upregulated in mice infected with *Helicobacter pylori* [110]. Similarly, RAW264.7 cells and human monocyte-derived macrophages (MDM) infected with Mtb showed elevated expression of *XIST* [111]. It also binds with miR125b-5p and represses its expression in macrophages. Mir125b-5p regulates NF-κB expression through A20, a suppressor of NF-κB. Thus, *XIST* upregulation by Mtb is expected to activate NF-κB expression and related proinflammatory responses in macrophages. Interestingly, macrophages treated with recombinant BCG expressing ESAT-6 or recombinant ESAT-6 protein show upregulation of *XIST* similar to that of Mtb-infected macrophages [111]. ESAT-6 is a secretory protein, immunogen, and a major virulence factor of Mtb that participates in various pathogenic mechanisms such as phagosomal rupture, prevention of antigen presentation, interaction with TLR-2, and others [112]. Thus, induction of *XIST* by ESAT-6 indicates that Mtb modulates this lncRNA to induce proinflammatory responses and subsequent tissue damage during active TB.

4.10. LncRNA small nucleolar RNA host gene 16 (SNHG16)

It is one of the lncRNAs associated with lung cancer and adenocarcinoma, and the gene encoding this RNA is located in chromosome 17q25.1 [113]. Interestingly, *SNHG16* could be induced by LPS, indicating that it regulates inflammation [114]. The expression of *SNHG16* was found to be elevated significantly in TB patients compared to healthy controls; particularly, its levels could discriminate active TB from latent TB [115]. Further, THP-1 macrophages infected with Mtb also displayed increased expression of *SNHG16* in a dose and time-dependent manner, accompanied by increased proinflammatory cytokine secretion. Silencing of *SNHG16* expression reversed this

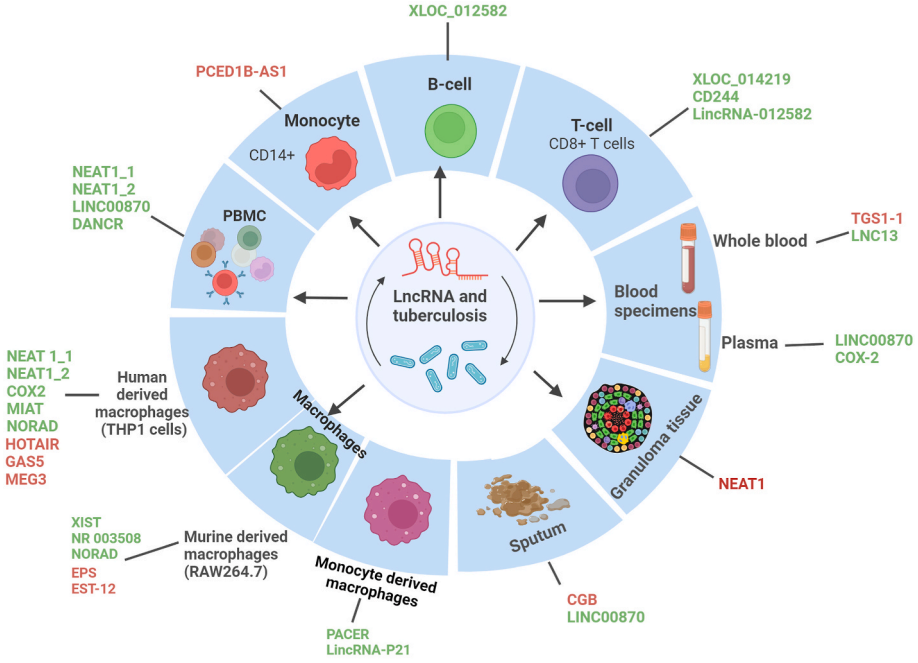

Fig. 2. Schematic showing up- and down-regulated lncRNAs in macrophages infected with *M. tuberculosis* or other mycobacterial species and their outcomes. Arrows within the boxes indicate the up or down-regulation of lncRNAs. Arrows outside the boxes indicate the directions and the possible outcomes of increased/decreased levels of cytokines. Abbreviations: Mtb, *M. tuberculosis*; KD, knockdown of expression. Mycobacterial infections in macrophages upregulate the expression of lncRNAs *lincRNA-COX2, NEAT1, XIST, SNHG16, NORAD, NR_003508, DANCR and MIAT* and down-regulates the expression of *HOTAIR, GAS5, PCED1B-AS1, MEG3, lincRNA-EPS and EST12*.

pattern, indicating its direct role in the induction of inflammatory responses [115]. It appears that *SNHG16* works through miR-140-5p to increase the inflammatory response, and in TB patients, the expression of miR-140-5p showed a negative correlation with *SNHG16* expression [115], indicating that it is an important regulator for the inflammatory response in TB patients.

4.11. LINC00870 or NR_038221

LINC00870 is one of the upregulated lncRNAs in the plasma of pulmonary TB patients [63]. The role of this lncRNA was further evaluated by infecting PBMCs with Mtb. Similar to plasma of TB patients, PBMC infected with Mtb exhibited elevated levels of *LINC00870*, accompanied by increased Th1 and Th2 cytokine levels [116]. The overexpression of *LINC00870* in these cells activated JAK/STAT pathways that control the immune response to infection [116]. Since *LINC00870* upregulates both Th1 and Th2 responses, it could be an important player in the immunopathogenesis of tuberculosis. Future research involving in vivo models may help understand its role better. However, the detectability of *LINC00870* in the plasma and sputum samples of TB and LTBI patients but not in the plasma and sputum of healthy controls may be interesting. This characteristic attests to its utility for developing a TB diagnostic tool.

4.12. LincRNA XLOC014219 and XLOC_012582

The *lincRNA XLOC-014219* and *XLOC_012582* were found to be significantly upregulated in $CD8^+$ T cells and B cells, respectively, of patients with active pulmonary tuberculosis (PTB) [61,117]. While the expression of the *lincRNA XLOC-014219* showed correlation with its neighboring gene *HMOX1* encoding heme oxygenase 1 protein, the expression of *XLOC_012582* correlated with its neighbor *SOCS3* encoding the protein suppressor of cytokine signaling 3. These observations led the authors of these papers to propose that the upregulated HMOX1 and SOCS3 might be related to the exacerbation of the disease in these patients. However, this is only speculation, and experimental evidence for regulating *HMOX1* and *SOCS3* genes by the *lincRNA XLOC-014219* and *XLOC_012582* is unavailable.

4.13. LincRNA-P21

LincRNA-p21, located on chromosome 6p21.2, promotes P53-dependent apoptosis [118], a key defense mechanism against intracellular pathogens [118]. *LincRNA-p21* enhances apoptosis by upregulating its neighboring gene p21 while negatively regulating distant genes within the p53 transcriptional network, leading to p53-dependent cell cycle arrest and apoptosis in various cell types [118]. The *lincRNA-p21* expression levels increased in macrophages infected with Mtb and pulmonary TB patients' whole blood. Its levels decreased to those of healthy controls after six months of treatment, possibly indicating its utility as a biomarker for TB treatment [119,120]. However, its potential role in host-directed therapy needs to be explored.

4.14. LncRNA 13 (LNC13)

Long non-coding RNA 13 (*LNC13*), located on chromosome 2q12.1, is linked to various diseases, including celiac disease, type 1 diabetes, and inflammatory bowel disease [121]. *LNC13* is believed to modulate inflammatory gene expression through interactions with proteins such as hnRNPD and HDAC1, which influence chromatin dynamics and transcriptional regulation [122]. Its expression levels are notably elevated in patients with active pulmonary tuberculosis, indicating its involvement in the immune response to Mtb [121]. As treatment progresses, *LNC13* levels decrease, suggesting it could be a biomarker for monitoring disease activity and treatment efficacy [121]. Investigating the precise mechanisms by which *LNC13* regulates immune responses could yield valuable insights into developing new therapeutic approaches.

4.15. Homeobox transcript antisense RNA (HOTAIR)

HOTAIR is an imperative polyadenylated and spliced lncRNA that involves 6 exons and 2158 nucleotides [123]. Overexpression of *HOTAIR* was first discovered in breast cancer patients, where it facilitates genome-wide retargeting of polycomb repressive complex 2 (PRC2), which in turn promotes metastasis and invasion of breast cancer cells [124]. The PRC2 complex affects the epigenetic transcription of genes by methylating H3K27me3 [125]. Its potential role in regulating apoptosis, cell cycle, autophagy, self-renewal, and metabolism of cancerous cells against chemotherapy has been established [126]. A study has reported that *HOTAIR* was deregulated in H37Rv-infected THP-1 macrophages but upregulated in H37Ra-infected macrophages. It appears the down-regulation of *HOTAIR* enhanced the expression of dual specificity phosphatase 4 (*DUSP4*) and special AT-rich sequence--binding protein 1 (*SATB1*), which promoted the survival of Mtb H37Rv *M. tuberculosis* in macrophages [21,127]. Thus, it seems that Mtb exploits *HOTAIR* to survive within macrophages, and *HOTAIR* could be manipulated to decrease the survival of Mtb in macrophages.

4.16. Commensal bacteria-associated (CGB) lncRNA

Recent literature indicates that the gut microbiome could modulate immunity at distant sites such as the lungs, and gut dysbiosis results in systemic inflammation [128,129]. A commensal bacteria-associated *CGB lncRNA/ENSMUSG00000086503*), which participates in the interaction of intestinal epithelial cells to gut microbes, is highly downregulated in TB patients and in mouse models of TB infection [130]. In fact, *CGB* interacts with enhancers of zeste homolog 2 (*EZH2*) and negatively regulates methylation of H3K27Me3, leading to increased IFN-γ expression [130,131]. IFN-γ is a crucial cytokine associated with protection against TB, and studies have reported that mice deficient in IFN-γ are susceptible to Mtb infection [132]. Hence, it is logical to speculate that Mtb downregulates *CGB* to survive and establish infection in the host. This hypothesis is supported by the observation that *CGB* genomic knockout (KO) mice manifest more severe TB disease than the control mice [130].

4.17. Transcriptional gene silencing 1 (TGS-1)

TGS-1 lncRNA is located on chromosome 8 with 2 exons. An investigation revealed that *TGS-1* was significantly downregulated, and its target miR-143 was upregulated in TB patients compared with healthy individuals [133]. miR-143, in turn, regulates the expression of *COX-2* which is associated with inflammation [134]. *TGS-1* is likely related to increased inflammation in TB patients; however, this warrants additional investigations. Interestingly, the SNP genotyping study discloses that *TGS-1* genetic variants are associated with the severity of TB infection, leading to thrombocytopenia in the Western Chinese population [133]. More studies are required to uncover its role in TB pathogenesis.

4.18. PC-esterase domain containing 1B-antisense RNA 1 (PCED1B-AS1)

The *PCED1B-AS1* has been linked to promoting renal carcinoma and pancreatic ductal adenocarcinoma, indicating its role in cancer progression [135,136]. The expression of this lncRNA in $CD14^{+}$ monocytes of active tuberculosis patients was down-regulated compared to healthy controls. Additionally, it has been reported that this down-regulation correlated with reduced apoptosis and increased autophagy, and this phenomenon could be confirmed by the knocking down of *PCED1B-AS1* in macrophages in vitro. Further, it seems that the *PCED1B-AS1* exerts its effect through miR155, which is capable of suppressing apoptosis and enhancing autophagy by targeting FOXO3 and Rheb, respectively [137,138], as overexpression of FOXO3 and Rheb in macrophages abolished the effects of *PCED1B-AS1*. This indicates that Mtb suppresses this lncRNA strategically to evade killing by apoptosis and spread to other cells through necrosis.

4.19. LincRNA erythroid pro-survival (LincRNA EPS)

The *lincRNA EPS*, better known as *Ttc39aos1*, was initially identified in mouse erythropoiesis and has since been recognized for its role in controlling transcriptional regulators of the inflammatory system [139]. In its native physiological state, *lincRNA EPS* is highly expressed in resting macrophages, where it plays a critical role in modulating nucleosome positioning and repressing the transcription of immune response genes (IRGs) and genes involved in inflammation and apoptosis. While the knockout of *lincRNA EPS* in mouse macrophages led to an unrestrained inflammatory response in vivo, the knockdown of *lincRNA EPS* resulted in apoptosis in vitro [139,140]. Interestingly, *lincRNA EPS* was found to be downregulated in response to inflammatory stimuli such as lipopolysaccharides (LPS), indicating that it has a role in regulating inflammatory responses [141]. Further, studies have shown that *lincRNA EPS* deficiency or its knockout in macrophages contributed to host protection against viral infections at basal levels and upon induction [142]. There is growing interest in investigating the association between *lincRNA EPS* expression and tuberculosis (TB) infections, and a study has revealed that *lincRNA EPS* was downregulated in the monocytes of active pulmonary patients in relation to healthy individuals. In vitro, the knockdown of *lincRNA EPS* in RAW264.7 inhibited apoptosis in macrophages, but their infection with BCG enhanced autophagy through the JNK/MAPK signaling pathway [22,143]. *LincRNA EPS* is an important lincRNA associated with the pathogenic mechanisms of Mtb.

4.20. Early secreted target with a molecular weight of 12 kDa (lnc-EST12)

Lnc-EST12, spanning 1583 base pairs, demonstrates a distinctive expression pattern primarily in immune-related organs such as the liver, lung, and spleen under physiological conditions and regulates proinflammatory cytokines [144]. Its expression was significantly downregulated in mouse macrophages upon infection with Mtb, and this was attributed to the suppression exerted by EST12, a 12 kDa secretory protein of Mtb, through the JAK2-STAT5a signaling pathway [144]. Mouse macrophages treated with EST12 have shown downregulation of *lnc-EST12* in a dose and time-dependent manner, and macrophages from *lnc-EST12* knockout mice activated the NLRP3 inflammasome and GSDMD-mediated pyroptosis by interacting with transcription factor FUBP3 [144]. Additionally, these macrophages efficiently cleared the Mtb infection and increased inflammatory responses, indicating that Mtb negatively regulates *lnc- EST12* to suppress the antimycobacterial response. This elegant mechanism to suppress innate immunity for its survival within macrophages is a classic example of the intricate regulatory networks underlying host-pathogen interactions. Interestingly, this finding may be the first evidence that a bacterial-derived protein regulates lncRNA in the host.

4.21. Growth arrest-special transcript (GAS5)

The expression of *GAS5* is either downregulated or upregulated in various cancers, and it plays a vital role in suppressing cancer progression [145]. *GAS5* was significantly reduced in TB patients' serum samples compared to healthy controls, which showed a correlation with increased proinflammatory cytokines IL-1β, IL-6, and TNF-α [146]. Macrophages infected with Mtb also showed downregulation of *GAS5* expression and upregulation of inflammatory cytokines. Interestingly, the *GAS5* downregulation in THP-1 increased the cells' viability, which could be rescued by the overexpression of *GAS5*, possibly indicating that Mtb modulates this lncRNA to survive longer within macrophages. The

longer viability appears mediated by miR-18a-5p, for which *GAS5* acts as a molecular sponge [146]. Subsequent investigations have shown that overexpression of *GAS5* inhibits the inflammatory response in Mtb-infected macrophages, potentially by downregulating miR-144-3p, a known target for *GAS5* [147]. These findings collectively suggest that *GAS5* is an important lncRNA determining the pathogenesis of Mtb [146,147].

4.22. *MIR99AHG*

The *MIR99AHG (Mir-99a-Let-7c cluster Host gene)* was one of the differentially expressed lncRNAs in mouse macrophages (BMDMs) stimulated with IL-4/IL-13 [148]. It showed the highest expression, over fortyfold than the control, in BMDMs upon stimulation with IL-4/IL-13 but exhibited severe repression in BMDMs infected with Mtb HN878 [148]. Human MDMs and mice infected with Mtb HN878 also showed similar repression of this lncRNA [148]. ASO treatment of MDMs and mice against *MIR99AHG* showed reduced intracellular and in vivo bacterial burdens [148], indicating that this lncRNA is a potential candidate for host-directed therapy for treating TB.

5. Genetic variations in LncRNAs and tuberculosis susceptibility

Genetic variation or DNA sequence variance based on Single Nucleotide Polymorphisms (SNPs) has been the basis for identifying the risk and susceptibility loci or disease-associated genes for several diseases [149]. Initial studies targeted only genes coding for selected proteins. However, advancements in genome sequencing have facilitated Genome-Wide Association Studies (GWAS) to identify disease-associated genes for many diseases [150]. GWAS studies for TB have revealed that variants in eight protein-coding genes, *JAG1, DYNLRB2, EBF1, TMEFF2, CCL17, HAUS6, PENK*, and *TXNDC4,* could confer susceptibility to TB [151]. Since lncRNAs play crucial roles in regulating protein-coding genes, some recent studies have investigated whether genetic variants specific to lncRNA genes are related to TB susceptibility or risk of TB (Table 2). *NEAT1*, which regulates proinflammatory response and is upregulated in TB patients, is one of the lncRNA genes selected for determining the role of SNPs in susceptibility to pulmonary TB (PTB) [152]. This study evaluated four SNPs (rs223895, rs3741384, rs3825071, and rs5122715) and found no statistically significant allelic frequency, indicating that variants of *NEAT1* have no association with the risk of developing PTB. Similarly, analysis of SNPs rs12427129, rs1899663, rs4759314, and rs7958904 related to *HOTAIR* and SNPs rs1055472 and rs11058000 related to *THRIL* in PTB showed no association for susceptibility or risk to TB [153]. The *HOTAIR* and *THRIL* regulate TNF-α [124,154], which may have roles in inflammation as *NEAT1*. However, an analysis revealed that SNP rs12333784 related to *AC007128.1* showed a significant risk for PTB and extrapulmonary TB (EPTB) in the Han Chinese population [155]. Interestingly, testing of two other SNPs, rs6463794 and rs720964, related to *AC007128*.1, showed no significant association with TB. Although the lncRNA *AC007128*.1 showed upregulation in these patients, it is unclear whether it modulates the immune response. However, there is speculation that this lncRNA could regulate immune response through G-protein coupled receptor signaling (GPGR) [155].

In addition to the above, SNP variants of *AC079767*, which confers susceptibility to TB in the Western Chinese Han population, were also examined [156]. No significant risk association was seen with variants rs10178277, rs1055228, and rs1055229, although variant rs2477677 showed a slight association with TB risk. Despite no relationship with TB risk, the variants rs2477677 and rs1055229 seemed to have some influence on the clinical presentations of TB. Similarly, seven SNP variants (rs2542670, rs1051838, rs1416, rs4262994, rs12939622, rs8075185, and rs2688) for *HNF1B3:1* had no significant association with TB risk [157], though the variants rs12939622, rs4262994 and rs2542670 showed some association with clinical manifestations. In contrast, an SNP variant rs7836840 of the *CASC8* had a significant association with susceptibility to TB in the Western Chinese Han population [158]. Three other variants (rs7825118, rs9297758, and rs6981424) of the gene were noted to have some association with clinical manifestations. Furthermore, a study has investigated the SNPs rs4737420 and rs111352767 of *TGS1-1* and *lnc-AC145676.2.1–6*, respectively, in Chinese TB patients [133]. The SNP rs4737420 was associated with a decreased risk of leukopenia, while no association was seen with SNP rs111352767. Overall, these findings collectively suggest that genetic variations in lncRNAs affect TB susceptibility or clinical presentation of TB to some extent. Further research is needed to elucidate the functional significance of these SNPs and their impact on immune regulation or TB pathogenesis. Likely, understanding the genetic basis of TB susceptibility could potentially lead to the development of personalized treatment of TB.

6. Summary and future perspectives

Tremendous progress has been made in comprehending the roles of lncRNAs in TB pathogenesis during the last five years. Most studies have used the blood samples of TB patients as the source for the lncRNAs, obviously due to the limitations in collecting other tissues from humans. However, sufficient consideration has been given to analyzing the expression of lncRNAs in individual components of the blood, such as plasma, serum, PBMCs, T cells, B cells, etc. (Table 1 and Fig. 1). Interestingly, each of these tissues has shown a specific pattern of lncRNA expression, consistent with the notion that the expression of lncRNAs is tissue-specific [159,160]. Unfortunately, these tissues/samples have shown differential expression of many lncRNA genes [57–68], making their characterization difficult. Further, the functions of many of the differentially expressed lncRNAs in tissues are currently unknown, particularly those that are highly up or down-regulated. A limited number of studies have attempted to characterize the role of new lncRNA genes to some depth [116,117,144]. The above restrictions limit our understanding of lncRNAs, which may play crucial roles in the pathogenesis of TB. Though this is partly due to the infancy of the lncRNA field, analysis of the functions of the differentially expressed lncRNAs using appropriate models would provide a deeper understanding of their role in the pathogenesis of TB. Thus, future studies should focus on determining the functions of the differentially expressed lncRNAs.

Remarkably, the characterization of selected differentially expressed lncRNAs in TB, reviewed above, has revealed that many have a role in innate or adaptive immunity. Some of these lncRNAs target autophagy, apoptosis, or necrosis pathways. Previously, several studies have reported that Mtb modulates these pathways for survival and dissemination of infections, and several surface components and secreted effector proteins are implicated in this process [161,162]. Notably, a surface cell wall lipid lipoarabinomannan [163] and secreted proteins ESAT-6 and CFP-10, encoded by the RD1 region [161], are the key players in Mtb's immune evasion and immunopathogenesis. In this context, it is relevant to suggest that the role of lncRNAs in the pathogenesis may be better understood by infecting macrophages with Mtb mutants lacking these components. Similar studies with Mtb mutants lacking effector proteins, such as SapM, ZMP1, PtpA, and pknG, that interfere with phagolysosomal fusion will facilitate the identification of novel lncRNAs regulating this pathway [162]. As noted, phagosomal maturation arrest in phagocytes is a critical pathogenic mechanism of Mtb to survive and replicate in the intracellular compartments. Identification of lncRNAs modulating this event could potentially lead to the development of new therapeutic strategies. The feasibility of the proposed studies is supported by the differential expression of lncRNA genes by recombinant BCG expressing ESAT-6 and EST-12, a secreted protein of Mtb [111, 144]. Further, Mtb clinical isolates varying in pathogenicity could also help uncover novel lncRNAs regulated by Mtb in the host.

On the other hand, the alteration of lncRNA expression related to

adaptive immunity by Mtb is highly relevant to the development of therapeutics for TB. The expression of these lncRNAs can be modulated by specific tools, leading to faster Mtb clearance [144]. It has already been shown that some lncRNAs reviewed in this article could be modulated by antisense si-RNA technology. In fact, one study has demonstrated that bacteria can efficiently be eliminated in a mouse model of infection by modulating the lincRNA [148]. This is remarkable and paves the way for host-directed therapy for TB by targeting lncRNAs, particularly those infected with drug-resistant strains of Mtb. With the latest advancements in gene-editing tools such as antisense oligonucleotides (ASOs) or CRISPR/Cas9-based approaches, lncRNA-based therapies show great promise for TB treatment. However, developing an efficient drug delivery system remains a challenge, with issues like sequence-induced toxicity [126]. To overcome this, novel therapeutic vaccines that induce or suppress specific lncRNAs can be engineered and administered. Thus, lncRNAs related to adaptive immunity will remain a new platform for treating TB in the future.

In addition to therapy, lncRNAs could play a more significant role as biomarkers for diagnosing and treating TB. Many studies have focused on this front and have identified some candidate lncRNAs reviewed in Refs. [23,25]. However, their utility needs to be validated with different populations. Because lnRNAs are used to diagnose and treat diseases such as cancer, lncRNA-based diagnostics are likely to revolutionize TB treatment. One area where lncRNAs could potentially contribute is in HIV-TB coinfection. Due to disease complexity, diagnosis of TB in HIV people is difficult with available techniques [164]; hence, lncRNA-based diagnostics are highly desirable. We have already identified some novel lncRNAs that can distinguish HIV-TB from HIV infection [165]. This is very encouraging, and we believe future studies on lncRNAs in TB will increase our understanding of the pathogenesis of TB but also its diagnosis and treatment.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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