· Review ·

Research progress regarding *Mycobacterium tuberculosis* and its related small RNAs in the prevention and regulation of tuberculosis

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Abstract

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), continues to pose a significant global health challenge, particularly in developing regions. This review highlights the ability of MTB to evade host immunity and establish latent infections, which is intricately linked to its regulatory mechanisms, including small non-coding RNAs (sRNAs). These sRNAs play crucial roles in modulating bacterial stress responses, metabolism, and virulence, thereby enhancing the survival of MTB in hostile environments. Recent advances in sRNA detection techniques, such as northern blotting and RT-PCR, have identified key sRNAs, including ASpks and ASdes, which appear to regulate lipid metabolism and immune evasion. Clinical studies have also suggested that sRNAs may serve as diagnostic biomarkers, potentially addressing the limitations of traditional TB diagnostic methods. Despite these advancements, this review underscores the need for further research to fully elucidate the regulatory potential of sRNAs in TB pathogenesis and to explore their applications in diagnostics and therapy.

Keywords: Tuberculosis, *Mycobacterium tuberculosis*, small RNAs, interaction

Tuberculosis (TB) is one of the most common serious infectious diseases worldwide and a major cause of respiratory diseases [1]. According to statistics released by the World Health Organization, approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB) [2]. In some developing countries, the carriage rate of MTB in adults is as high as 80%. Approximately 8 to 10 million new cases of TB are reported worldwide annually, resulting in approximately 1.4 million deaths [3]. In 2022, China was one of the countries with the highest incidence of TB in the world [4]. Approximately 130,000 patients die from TB each year in China, and the majority of TB patients reside in rural areas [3]. The National Tuberculosis Epidemiological Sampling Survey in 2000 showed that nearly half of the population was infected with MTB [5]. TB in China is characterized by high infection rates, high incidence rates, high mortality rates, high drug resistance rates, and a higher incidence rate among young and middle-aged adults [1, 5]. The occurrence of HIV/AIDS,

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which heightens susceptibility to TB, further increases the number of TB-related deaths.

As a result of its high adaptability to the human microenvironment and to treatment strategies, MTB has become a major threat to human health. Bacterial non-coding RNAs are a large class of RNA molecules with regulatory functions, which control various physiological processes through different mechanisms. These RNAs include riboswitches, CRISPR RNAs, and small non-coding RNAs (sRNAs). Among these, sRNAs are the most extensively studied class of post-transcriptional regulatory factors [6]. sRNAs might help MTB to survive the hostile microenvironment within macrophages. This review summarizes the mechanisms of sRNA-mediated regulation in MTB, how sRNAs affect mycobacterial pathogenesis, and sRNA detection in the host.

Mycobacterium tuberculosis

MTB is a narrow, slightly curved bacterium measuring (1–4) μm × 0.4 μm. The bacterium possesses a capsule, but lacks spores, flagella, and endotoxins/exotoxins. The genome of MTB standard strain H37Rv is approximately 4.411 Mbp, with a G+C content of 65.6%. MTB is a typical intracellular pathogen that is mainly transmitted by droplets into the distal respiratory tract, where it is subsequently engulfed by alveolar macrophages [7]. Most studies have shown that MTB can colonize cells for long periods of time and even spread to other cell types [7]. MTB can induce various immune responses in host cells, but the regulatory mechanisms of these responses require further investigation.

Pathogenicity and immunity of MTB

Upon inhalation and infection, MTB encounters a variety of lung microenvironments, both extracellular (becoming reactivated in cavities or after escaping necrotic cells) and intracellular (within alveolar phagocytes like alveolar macrophages) (Figure 1) [8]. After being inhaled into the respiratory tract, MTB is engulfed by alveolar macrophages, in which it can survive for a long period of time. In response to MTB infection, cells secrete a variety of cytokines, such as interferon-γ (IFN-γ), vitamin D, and tumor necrosis factor-α (TNF-α). These cytokines play an important role in the activation of macrophages to kill MTB. Studies have shown that IFN-γ can kill MTB by inducing autophagy, whereas TNF-α enhances the bactericidal activity of macrophages via activation [9, 10]. In addition, MTB infection is also closely related to the immune regulatory mechanism of the host, manifested as the activation of immune cells, the secretion of immune molecules, and the activation of immune signaling pathways. However, MTB, as one of the most successful intracellular parasites, has developed the ability to resist host cell killing during its evolution to establish latent infection. The MTB in phagocytes can inhibit the transport of hydrolase and H+-ATPase subunits from the Golgi apparatus to the lysosome, thereby weakening the acidification of autophagosomes and preventing their degradation by host cells [11, 12]. Mannose-capped lipoarabinose in the cell wall of MTB can inhibit the occurrence of autophagy by regulating the intracellular vesicle transmission pathway and the proteins related to autophagosome maturation, such as LAMP1, Cts1, TfR, and EEA1 to hinder the clearance and killing effects of host cells [13-15]. In addition, MTB enhances the phosphorylation of an amino-terminal kinase (JNK) that is specific for enhanced intracellular survival (Eis) protein. As JNK is an activator of Beclin 1, an important regulatory protein for autophagy activation, Eis protein can also inhibit the occurrence of autophagy [16, 17]. In addition, the early secretion targeting antigen (6 kDa) of MTB (early secretory anti-target 6, ESAT6) and the culture filtrate protein (10 kDa, CFP10)

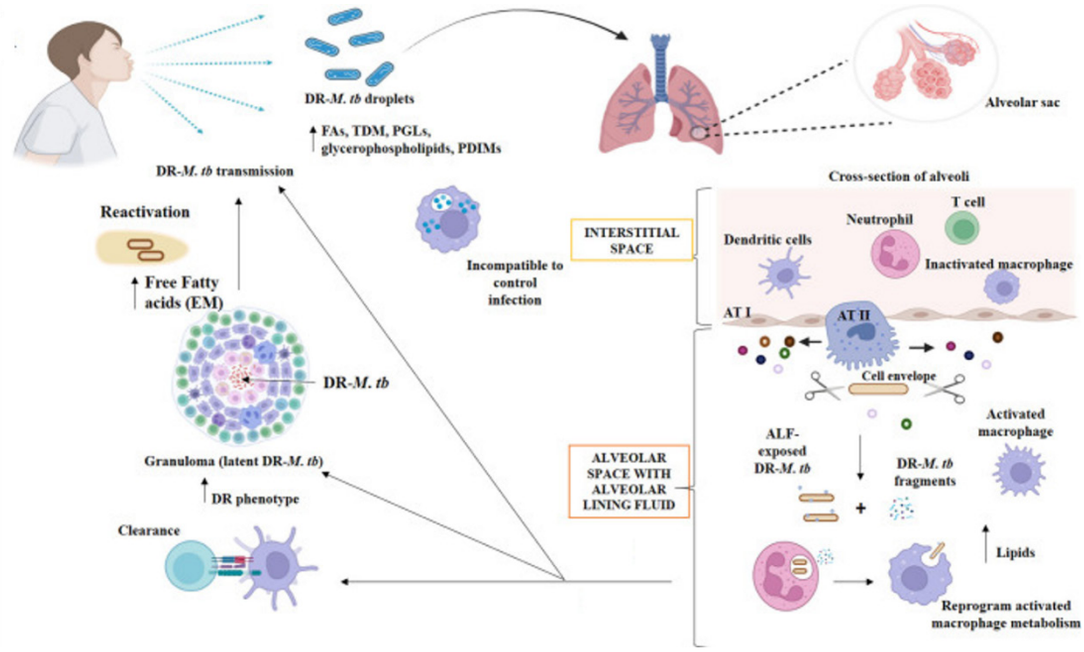

Figure 1. Interactions between drug-resistant MTB and the host at various stages of infection in the pulmonary microenvironment [8].

can inhibit the clearance of intracellular MTB by autophagy by inhibiting the maturation of phagocytes to autophagic lysosomes [18]. Protein kinase G of MTB can also phosphorylate host proteins to inhibit the maturation of autophagic lysosomes [19]. MTB hijacks the maturation and transport of autophagic lysosomes in host cells through a series of mechanisms (mentioned above), thereby avoiding their digestion and degradation by host cells, as well as antigen presentation, allowing MTB to evade clearance and killing by host cells and develop a latent infection.

Bacterial sRNA

Bacterial sRNA is a small regulatory RNA molecule with a length of approximately 50 to 300 bp, which plays an important role in the post-transcriptional regulatory network in bacteria. sRNA mainly plays a biological role through incomplete base complementary binding to mRNA molecules and direct binding to protein. sRNA can mediate the response of bacteria to environmental stress and regulate their growth, metabolism, virulence, and stress adaptability. The recent discovery of novel sRNA target genes has become key in the study of their physiological functions.

Bacterial sRNA was discovered in 1984 when MicF RNA of 174 nt in length was first detected in *Escherichia coli* and this sRNA was found to inhibit OmpF protein on the outer membrane. Early sRNA findings relied primarily on multicopy phenotypes, gel analysis, or unexpected discoveries. However, these methods have significant limitations in systematically detecting new sRNAs. From 2001 to 2002, four studies reported the prediction of sRNA promoter and terminator sequences in *Escherichia coli* using *in silico* methods, which made the discovery of new sRNAs more systematic [20]. Subsequently, the application of experimental methods such as cloning technology and inter-gene probe microarrays have further promoted the identification of sRNAs. These methods are applicable not only to E. coli but also to other bacterial genomic sequences, resulting in an increasing number of bacterial sRNAs being identified.

Prediction of sRNAs in *Mycobacterium* spp.

To date, sRNA studies of *Mycobacterium* spp. have mainly focused on MTB and *Mycobacterium bovis* BCG. In 2006, Livny *et al.* [21] used the sRNAPredict2 software to predict the sRNAs of 56 MTB strains without experimental verification. In 2009, by establishing a library sequencing method, researchers found five trans-encoded antisense sRNAs and four cis-encoded antisense sRNAs in MTB [22]. Along with improvements in bioinformatic methods and experimental tools, researchers have now identified more than 100 additional sRNA species in MTB. Recent studies have mainly focused on the discovery of these sRNAs and their expression changes in bacterial stress responses. For example, sRNAs F6 affects the expression of the essential chaperonins GroEL2 and GroES, associated with long-term survival of M. tuberculosis in human granuloma [23]. sRNA ASpks is highly expressed under oxidative stress, whereas sRNA ASdes is transcribed into DesA1 mRNA, which is complementary to DesA1 mRNA, and may be involved in the regulation of bacterial fatty acid metabolism [22]. Although these studies provide important clues for understanding the function of sRNAs, specific functional studies of sRNAs of MTB in vivo remain preliminary. Mcr7 is the first MTB sRNA to be confirmed functionally to regulate the mRNA expression of TatC, thus affecting the secretion of TAT protein, and ultimately the expression of the immunodominant proteins Ag85 and BlaC [22].

The mode of action of bacterial sRNAs

Interaction with mRNA: When the sRNA-mRNA binding site is located between 15 nt upstream and 20 nt downstream of the mRNA initiation codon, sRNA can directly bind to the ribosome binding site of mRNAs and inhibit translation initiation (Figure 2). In recent years, studies have reported other mechanisms by which sRNA inhibits mRNA translation, such as inhibition of the translation process by binding to a redundant ribosome binding site, an upstream open reading

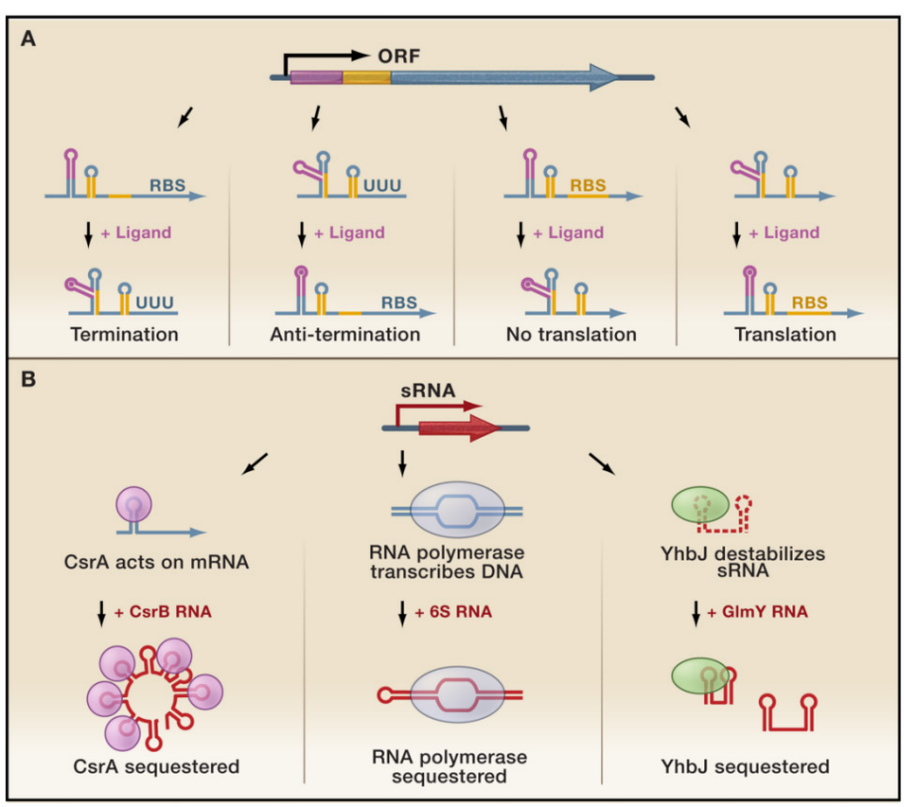

Figure 2. Gene arrangement and regulatory functions of ligand- and protein-binding regulatory RNAs [6]

frame, or a translation enhancer. These findings have further enriched our understanding of the regulatory mechanisms of sRNAs.

Effect of sRNA and protein: The molecular chaperone Hfq plays a key role in the regulation of trans-encoded sRNAs [24]. Hfq can increase the base pairing between sRNA and mRNA, thereby enhancing the regulatory effect of sRNA. Hfq is also important for maintaining the stability of sRNA in vivo [25]. However, studies have shown that the regulation of sRNA by Hfq is not significant in gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus*. In addition, a type of cis-encoded sRNA (ranging from 100 to 7000 nt) exists in bacteria, which can be completely complementary to the target mRNA, and such sRNAs play a regulatory role in transcription and translation, and affect mRNA stability. In addition, one class of sRNAs bind to and regulate the activity of nucleic acid-binding proteins by mimicking homologous protein targets. Recent studies have also revealed a class of bifunctional sRNAs that not only pair with one or more regulatory targets, but also encode small molecular proteins [26]. For example, SgrS sRNA in *E. coli* can inhibit mRNA translation by base pairing, and also directly repress transporter activity by encoding an SgrT protein [27].

Mechanism of action of bacterial sRNAs

sRNAs play an important role in bacterial pathogenicity, metabolism, quorum sensing, and stress responses [28]. sRNAs are usually regulated by transcription factors related to specific environmental or metabolic signals, and many sRNAs can simultaneously regulate the expression of multiple targets, and some even serve as overall regulators of bacterial stress responses. However, the mechanism of action of sRNAs on host cells remains unknown. In recent years, cross-species small RNA transmission has become a hot research topic. Viruses regulate gene expression in the host via encoded microRNAs, and circulating viral microRNA is found in human serum, plasma, saliva, and urine [28, 29]. Epstein–Barr [30] virus-infected B cells can secrete viral microRNAs into uninfected cells through exosomes, and the microRNAs can inhibit the expression of the cellular immune gene CXCL11 [31]. In addition, the sRNA of *Botrytis cinerea* is present in infected *Arabidopsis* plants and contributes to infection by selectively silencing host immune genes by binding to AGO1 in the RNAi system that hijacks the host [32]. These examples of cross-species transmission of sRNA suggest that bacterial sRNAs may also affect host cells through a similar mechanism during infection. Therefore, the specific role of the sRNAs of MTB in humans remains an important topic for future research.

Laboratory methods for the analysis of bacterial sRNAs

At present, there are two main methods for experimental verification of predicted sRNAs, namely northern blotting and fluorescent quantitative PCR (FQ-PCR).

Northern blotting is a key technique for obtaining evidence of sRNA expression and a standard method for quantitative determination of sRNA in the absence of amplification. Northern blotting is considered by many researchers to be the gold standard for the identification of sRNA. For example, 22 of 228 sRNAs have been validated in Agrobacterium tumefaciens by northern blotting [33]. However, the disadvantage of northern blotting is the large number of samples required to avoid false positives. The small quantities of sRNA in bacteria, its susceptibility to degradation, and the high cost of sample preparation, mean that northern blotting has certain limitations in practical application.

FQ-PCR is often used for the identification of sRNA,

and can detect sRNA molecules at low abundance with high sensitivity compared with northern blotting. However, the complex secondary structure of bacterial sRNA means that the FQ-PCR method is susceptible to contamination and the generation of false positives. In addition, the procedure is relatively complex and costly. Nevertheless, FQ-PCR has some value in terms of sRNA detection, especially when high sensitivity is required.

The gradient RT-PCR method is highly sensitive, and even a trace amount of RNA can be used to establish a cDNA library followed by PCR amplification, electrophoresis of the amplified products, and sequencing verification. This method converts trace RNA into high-content DNA, and has the advantages of easy operation, low cost, and a low probability of false positives. The RT-PCR method is of great significance for the detection of bacterial sRNA in the laboratory, providing a basis for studying the function and targeting mechanism of sRNA.

Detection of sRNAs in MTB-infected patients

MTB can exist in cells for a long time after it is transmitted into the human body through droplets. Bacteria may secrete sRNA into the human body, and thus affect the physiological processes of the host. At present, the main method employed for the clinical diagnosis of TB is a sputum smear, but the positive detection rate using this method is low, at only ~33%. The positive detection rate using a culture method can reach ~40%, but this method is time-consuming. Clinicians usually carry out clinical diagnosis of TB by combining imaging techniques, such as a chest radiograph or chest CT, with laboratory test results such as the erythrocyte sedimentation rate, purified protein derivative, and TB antibody levels. However, these methods have low positive detection rates, high rates of misdiagnosis, and are time-consuming to complete. Therefore, it is necessary to find new diagnostic methods.

We detected sRNA in the peripheral blood plasma of patients and controls and identified four sRNAs: ASpks, ASdes, AS1890, and AS1726 [34]. ASpks is an antisense transcript that aligns with mRNA, it is 75-nt in length and encodes the same ketosynthase domain as that within the pks12 gene [35]. The pks12 gene is involved in that synthesis of mannosyl-β-1-phosphoketolase molecules and ASpks, which is recognized as an antigen restricted by cd1, has the potential to act as a cis- or trans-encoded sRNA, depending on the boundary of the sRNA. ASpks displays regions of significant complementarity within pks7, pks8, and pks15, suggesting potential regulatory effects on the expression of these genes involved in polyketone synthesis. ASdes can act as a cis- or trans-encoded sRNA to regulate the expression of desA1 and desA2 [34]. Fatty acid desaturases with significant complementarity to desA1 (Rv0824c) are essential for MTB growth and are upregulated in infection. ASdes was also identified with desA2 (Rv1094) for the desaturase gene, suggesting a potential regulatory role in the metabolism of lipids. AS1890 is an sRNA of 36 nt in length that is found in MTB. AS1726 is another sRNA identified in MTB of 27 nt in length. Recently, levels of all the 20 sRNAs annotated in MTB genome were detected in the plasma of TB patients, and three of them (MTS2823, MTS0997 and MTS1338) have the potential to be plasma biomarkers [36].

Conclusions

TB remains a significant global health threat, especially in developing countries, with high infection, incidence, and mortality rates. MTB, the causative pathogen, is a highly adaptable intracellular bacterium that evades host immune responses, enabling long-term

survival and latent infection. Critical to its adaptability are sRNAs, which regulate bacterial stress responses, virulence, and metabolism. Recent research highlights the regulatory mechanisms of sRNAs in MTB, including their roles in immune evasion and pathogenesis (Figure 3). Advances in sRNA detection methods, such as northern blotting, FQ-PCR, and RT-PCR, have improved our understanding of sRNA functions. Clinical studies have identified specific sRNAs (e.g., ASpks, ASdes) in TB patients, suggesting potential diagnostic and therapeutic applications. However, further research is needed to fully elucidate the roles of sRNAs in MTB–host interactions and their potential as biomarkers or targets for TB management.

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Author Contributions

Zheng Wu and Wenjing Li wrote the manuscript. All authors read and approved the final manuscript for publication.

Conflicts of Interests

The author declares no conflict of interest.

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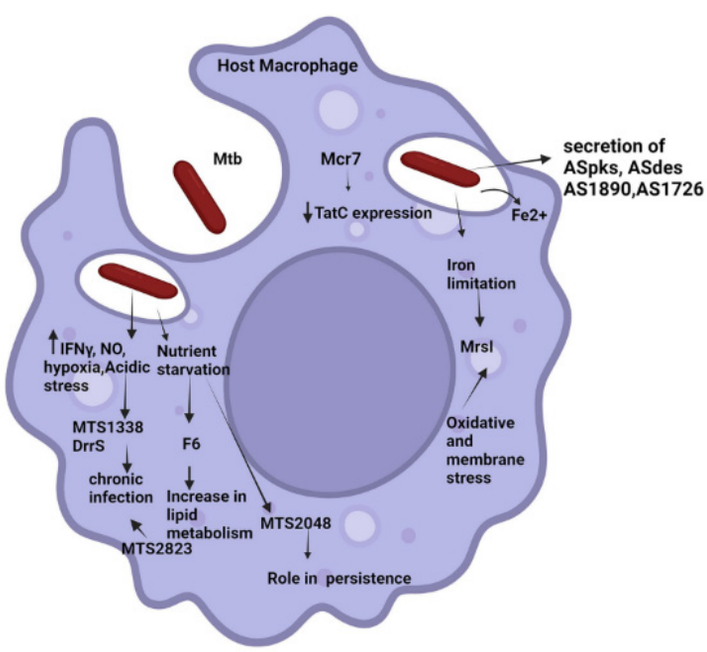

Figure 3. Potential regulatory roles of mycobacterial small RNAs in the host [37].

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