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Review Article

Influence of Respiratory and Gut Microbiome on the Outcome of Tuberculosis: A Comprehensive Review

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I N F O

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A B S T R A C T

Tuberculosis (TB) which is caused by the acid-fast bacterium *Mycobacterium tuberculosis* remains a major health challenge, affecting millions of people globally. It also remains a significant cause of morbidity and mortality specifically in countries with low and middle income. Recent research has shed light on the complex interplay between the human microbiome and TB, more particularly the respiratory and gut microbiota. Both respiratory and gut microbiome plays a regulatory role both in the incidence and progression of the disease. The intensive treatment protocols adopted for the treatment of tuberculosis also cause a greater impact on microbiome dysbiosis. Immunomodulatory properties of the microbiota play a major role in limiting the progression of the disease from latency and help to reduce the incidence of tuberculosis. This methodical comprehensive review was conducted across various scientific databases including PubMed, Scopus and Google Scholar employing keywords like “tuberculosis and microbiome”, “microbiome and immunomodulation” and “microbiome and therapeutics”. Research studies published from 2017 to 2023 were included in this review. This comprehensive review aims to explore the influence of the respiratory and gut Microbiome on the outcome of tuberculosis, highlighting the role of microbial dysbiosis, immune response modulation and potential therapeutic interventions.

Keywords: Tuberculosis, Gut Microbiome, Respiratory Microbiota, Immunomodulation, Mycobacterium tuberculosis

Introduction

Tuberculosis remains a major cause of morbidity and mortality globally, especially in developing countries. According to the recent WHO report, 10.6 million people were affected with tuberculosis in the year 2021 and 1.6 million people have lost their lives. Also, WHO reports that the incidence rate of tuberculosis is augmented by 3.6% in the year 2021 compared to 2020 which clearly signifies that there is a reversal in the trend of a 2% decrease in the incidence of tuberculosis every year as documented for the previous two decades.[1] This increase is mainly because of the negative impact caused by the COVID-19 pandemic. Also, an increased incidence in many countries is due to the HIV co-infection.

Multidrug-resistant tuberculosis remains a major health crisis globally and causing a security threat. Moreover, approximately only 1 in 3 people harbouring drug-resistant TB were able to acquire prompt treatment in the year 2021. However, 74 million people with TB were saved between the years 2000 and 2021. The United Nations Sustainable Development Goals target is to end the TB epidemic by 2030.

The role of human indigenous microbiota has greatly impacted the perspectives of clinicians about microbes towards health and disease. There is a drastic change in the comprehension that microbiota which inhabits the human body ecosystem greatly benefits the host-microbial organisation. This includes the synthesis of essential host nutrients and conversion of certain nutrients into simpler compounds and also offers protection against various pathogenic microbes.[2] This microbiota greatly enhances the metabolic and immune function of the host. Any alteration in the host microbial ecosystem plays a major role in the pathogenesis of various diseases which in turn cause a pronounced impact on human health. The alterations of the host microbiota can be due to lifestyle changes and a few underlying diseases. Dysbiosis can also increase the susceptibility of the host to many infections and it greatly depends on the anatomical site where it resides. The unique and diversified human microbiome is responsible for various metabolic activities and holds several functions within each anatomical site. Therefore there arises a larger need to comprehend the diversity of the microbiota, their functions and their contribution towards health and disease. Thus the indigenous microbiota has changed the perception that these microbes can help maintain the homeostasis of the host system and help the host from the acquisition of various infectious diseases.[3]

This methodical comprehensive review was conducted across various scientific databases including PubMed, Scopus and Google Scholar employing keywords like “tuberculosis and microbiome”, “microbiome and immunomodulation” and “microbiome and therapeutics”. Research studies published from 2017 to 2023 were included in this review.

Respiratory Microbiome

Composition and Function of the Respiratory Microbiome

The lungs similar to any other anatomical site harbour bacterial complexity. The microbiota of the lungs are very active because the elimination and colonisation of the organisms happens during aspiration, cough and also during mucociliary clearance. The lung microbiota includes *Bacteroidetes, Actinobacteria, Proteobacteria* and *Firmicutes*. The genera include *Prevotella, Veillonella* and *Streptococcus*.[4] The lung microbiome triggers immune tolerance which in turn protects the host from any undesired inflammatory manifestations.[5] This event is moderated by the respiratory microbiota and the immune cells of the lungs. The microbial composition of the lung helps in maintaining the homeostasis and healthy status of the lungs. The close relationship between the microbiome of the lung and pattern recognition receptors (PRR) present in the host immune cells helps in recognising the microbial molecules. One of the PRRs is the Toll-like receptor (TLR). Activation of the PRRs would stimulate the engagement of ligands which in turn induces the expression of immune-related gene expression and this further stimulates the immune response against pathogens. Also, the respiratory microbiota regulates the function of the antigen-presenting cells and the T regulatory cells (Treg).[6] Studies on the lower respiratory microbiome have revealed that there exists a high prevalence of the *Anelloviridae* family in addition to the bacteriophages. Besides, the mycobiome is composed of the genera *Malassezia, Eremthecium* and *Systenostrema.* The family *Davidiellceae* family, common fungi of the upper respiratory tract is also found in low numbers.[7] The host-microbiome relationship greatly signifies positive interactions like mutualism or commensalism and negative interactions like antagonism.

Alterations in the Respiratory Microbiome During Tuberculosis

A disturbed lower respiratory tract microbiome can make the host more susceptible to tuberculosis. The microbiome disturbances in the various anatomical sites are due to various factors like infection, malnutrition and antibiotics. The changes also cause a reduction in the colonisation of the microbiome which further results in the loss of containment of pathogens that leads to disease. Studies reveal that the role of microbiome plays a major role in lung disease. The lung microbiota like *Streptococcus, Veillonella* and *Prevotella* produce increased metabolic concentrates like arachidonic acid and pro-inflammatory cytokines line Interleukin 17 (IL-17) which in turn activates the Th17

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lymphocytes. Pathogenesis of tuberculosis is controlled by the equilibrium of Type 1-helper cells (Th1) and Type 2-helper cells (Th2) responses. Further many predisposing factors are responsible for tuberculosis. This includes malnutrition, HIV, smoking, alcohol, alcohol, diabetes and pollution, for example, consumption of alcohol can cause dysbiosis of the microbiome of the gut like *Proteobacteria* and *Bacteroidetes*. Similarly, cigarette smoking can reduce the oral flora like *Porphyromonas, Neisseria* and *Gemella.* This will alter the permeability of the lumen and also result in the translocation of metabolites that modulate the inflammation process.[8] Individuals with *M.tb* infection show enrichment of *Streptococcus* and *Pseudomonas* as part of the lung microbiome.[9]

Modulation of Respiratory Microbiome as a Potential Therapeutic Approach

The Immunomodulatory effects can be brought out by administering postbiotics orally or intranasal but many researches have to be carried out. Besides, the lung microbiota can be modulated in a way by selectively eliminating the bacterial pathogens by employing the use of predatory bacteria, human monoclonal antibodies that help to neutralise the pathogenic bacteria and their products and the application of pathogenic strain-specific bacteriophages.[10]

Composition and Function of Gut Microbiome

The human gut microbiome includes a community of flora comprising viruses, bacteria, fungi, archeas and protozoa. They produce various metabolites and proteins in a specific environment.[11] Our human intestine harbours more than 1,500 species of flora and they get colonised within minutes after birth. This flora greatly establishes a symbiotic relationship with the epithelial and lymphoid tissue.[12] The predominant intestinal microbiota falls under the phyla *Bacteroidetes, Firmicutes, Actinobacteria* and *Proteobacteria*. This microbiota synthesises a variety of metabolites due to anaerobic fermentation of the dietary components and both the host and microbes also generate various endogenous compounds. The common metabolites generated include the short-chain fatty acids (SCFAs) that activate the immune cells which in turn triggers the immune response. Hence the complex ecosystem of the gut stimulates the immune response and causes the proliferation and differentiation of the epithelial cells to fight against various infectious diseases.

Gut Dysbiosis and its Association with Tuberculosis

Recent literature states that dysbiosis of the gut can compromise the immune function of the host against *Mycobacterium tuberculosis* infection. It increases the susceptibility and recurrence of tuberculosis. A recent study reported that the diversity of the gut microbiota greatly declined in pulmonary tuberculosis. Many species of *Bacteroides increased* in abundance during the course of tuberculosis treatment; however, there was a significant decrease in the order *Clostrdiales*. An extensive decrease in the gut microbiome was reported in people who had undergone anti-TB treatment when compared to people with latent TB and healthy individuals.[13] Individuals on anti-tuberculous drugs have an enriched population of *Fusobacterium, Prevotella* and *Erysipelatoclostridium*. However, genera like *Blautia, Lactobacillus, Coprococcus, Ruminococcus* and *Bifidobacterium* were found to be depleted in people on anti-tuberculous drugs when compared to individuals with latent tuberculosis.[14]

A recent animal study using the H37Rv strain caused a considerable change in the gut microbiota, especially the organisms belonging to the order Clostridiales. Also, many genera of the class Clostridia decreased including *Butyricicoccus, Peptococcus, Acetivibrio,* and *Alkaliphilus*.[15]

Gut Microbiome Modulation and its Effects on Outcomes of Tuberculosis

Recent studies give evidence that the administration of antibiotics can lead to dysbiosis of the gut microbiome and increased susceptibility of the host towards the pathogenic bacteria.[16] A recent study by Khan et al., clearly states why the host immune system fails to elicit immune response and protection against tuberculosis after prompt anti-TB treatment. The outcome of his experimental studies revealed that when the mice were treated with a combination of pyrazinamide and isoniazid or only with rifampicin it resulted in a significant dysbiosis.[17] The treatment with isoniazid or pyrazinamide increased the microbial population belonging to *Bacteroidetes*. However, rifampicin greatly depleted the *Firmicutes* population. This dysbiosis of the gut microbiome led to increased susceptibility to *M.tb* infection and a considerable rise in the load. Besides, this scenario was reversed by faecal microbiota transplantation.

Also, the animals that are treated with isoniazid and pyrazinamide combination resulted in impairment in the function of the alveolar macrophage, especially its bactericidal activity. These macrophages when extracted from these treated mice were investigated they exhibited a decrease in their respiratory capacity, ATP production and basal respiration and were found to be more tolerant to *M.tb*. In addition to all these events, cytokines like IL-1beta (β) and tumour necrosis factor-alpha (TNF-α) and the major histocompatibility complex II (MHC II) are also greatly decreased in M.tb infection.

Therefore studies suggest that induced dysbiosis and the change in the circulation of various metabolites produced

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by microbiota following the treatment with isoniazid/ pyrazinamide can greatly influence the functioning of the alveolar macrophages.[18] Together, studies confer that narrow-spectrum tuberculous drugs have an intense impact on dysbiosis and this in return has a negative impact on the defence mechanism of the alveolar macrophages against the tubercle bacilli. Hence, with these studies, we understand that even on prompt treatment and cure, dysbiosis can result in impaired macrophage activity which in turn leads to recurrence of the infection.

Another study by Shi et al. concludes that short-chain fatty acids (SCFAs) are essential in maintaining homeostasis as they trigger the release of certain pro-inflammatory cytokines with the assistance of the signal transduction pathway. Metabolomics studies reveal that a considerable decrease in the SCFAs in TB patients underscores their involvement in the pathogenesis of tuberculosis.[19]

Gut-Lung Axis on the Pathogenesis of Tuberculosis and Immune Response

The gut-lung axis encompasses various connections like the systemic, anatomic and nervous systems that help to mediate the exchange of microbial signals between the gut and the lungs. The primary connection between the lungs and gut is established by the transfer of microbiota through the oropharyngeal reflux.[20] Our body encounters multiple refluxes which result in the transport of a variety of bacterial communities from the gut to the upper respiratory tract and finally to the lungs via microaspiration. Also, the bacteria from the gut can be translocated to the bloodstream and lymphatic system. Furthermore, the bacteria present in the gut can be taken up by the dendritic cells and other antigen-presenting cells like macrophages and this in turn will help to prime the B and T cells. These sensitised immune cells then migrate to the lungs.[21] A study by Thevaranjan et al. elicits that the gut microbiota of old mice can trigger the inflammation of the lungs and senescence of macrophages.[22] Another study by Taif etal., emanates that fecal microbiome transplantation can elicit an improved Th1 response towards M.tb which inturn reduces the severity of the disease.[23] Also, few studies reveal that the short-chain fatty acids produced by microbiota can be utilised as substrates for the host cells and also they behave as signalling molecules between various host tissues.

Influence of Microbiome on Host Immune System During Tuberculosis Infection

A few studies done on the immunomodulation brought out by the microbiome present in distal sites. One animal study has revealed that the lack of a segmented filamentous bacterial population in the gut (SFB) can lead to severe forms of pneumonia caused by *Staphylococcus aureus*. The high bacterial load can cause modulation of pulmonary Th17 immunity and decreased levels of IL-22 in the BAL fluid.[24] Therefore modulation of the gut microbiome can regulate the immune responses associated with the respiratory tract and thereby can alter its susceptibility to many infections.[25]

The important risk factors that are responsible for TB susceptibility like malnutrition, diabetes mellitus, alcohol, smoking, HIV infection, polluted air, etc., can also bring out dysbiosis of the gut.[8] This in turn alters the biosynthetic pathway of the gut microbiota which further changes the microbiota of the lung and modulates the immunological effects. Besides, this will also prevent the colonisation of pathogenic organisms or loss of lung microbiota inducing lung disease.[26]

Studies done by Arias et al. revealed that mice that are fed with a high-fat diet exhibited severe proinflammatory responses which increased the animal's risk of developing TB. This can also impair the immunological response due to BCG vaccination in obese mice.[27] The authors have given a hypothetical fact that this immune modulation is due to the reduction in either *Firmicutes* or *Bacteroidetes* phyla ratio. This study also suggests that gut dysbiosis can alter the metabolism of SCFA which in turn can increase the individual's susceptibility to TB.[28] According to Namasivayan et al., animals with severe TB disease were enriched with microbiota belonging to *Lachonospiraceae* and *Clostridiaceae* and had decreased numbers of bacteria belonging to the family *Streptococcaceae*.[29]

Many studies highlight that gut dysbiosis has a direct impact on *M.tb* infection which supports the role of gut-lung axis and susceptibility towards tuberculosis. Recent human studies evidence that pulmonary TB infection can bring down the population of *Bacteroidetes*.[18,30,31] The population of these phyla was found to be decreased in patients with recurrent TB infection. Species belonging to *Proteobacteria* and *Actinobacteria* especially *Escherichia coli* were found to be increased in faeces of TB patients. Therefore, the phyla *Bacteroidetes* and the genera *Lachnospira* belonging to the phyla *Firmicutes* were found to be decreased in both recurrent and new TB patients when compared to the healthy controls.[32] Another study by Li et al. reveals that paediatric patients with pulmonary TB had a decreased microbial population. In patients with pulmonary tuberculosis, there was an upregulation of pro-inflammation-inducing bacteria like *Prevotella* and opportunistic pathogens like *Enterococcus.* However, there was a reduction in beneficial bacteria like *Ruminococcaceae, Bifidobacteriaceae* and *Faecalibacterium prausnitzii.* Anti-tuberculous treatment also causes gut dysbiosis. Therefore, all these clearly underscore that gut microbiota can affect the pathogenesis of pulmonary tuberculosis (PTB) and also cause de-regulation of the immune status of the host through the gut-lung axis.[33]

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A few studies claim that an increase in propionate and butyrate-producing intestinal bacteria has an inhibitory effect on the release of IFNγ and IL-17 A which in turn reduces the proliferation of Th17. This results in injurious dysregulation of the host immune response against TB infection. Furthermore, the induction of immunosuppressive Treg cells in the gut causes IL-10 release and this in the presence of butyrate can suppress the proinflammatory T cell responses in tuberculosis patients that induct chronic infection and immune evasion.[34]

Host Microbiome-Directed Therapies for Tuberculosis

Microbiome-associated therapies are directed with the use of probiotics. As an alternative approach, currently, prebiotics are also used to regulate the microbiome population and their function.[35] Prebiotics are substrates that are selectively utilised by the host microbiome to confer benefit to the host. The commonly employed prebiotics include inulin, galacto-oligosaccharides, fructo-oligosaccharides, lactulose etc. Since these prebiotics highly influence the gut microbiota their clinical benefits appear to be a capable therapeutic option. A study by Flesch et al. revealed that using a synbiotic combination of both probiotics and prebiotics is found to be more effective in reducing infection rates.[36]

Studies state that propionic acid and lactic acid bacteria are found to be highly effective in treating certain inflammatory diseases. Due to the bactericidal property of these lactic acid bacteria, these probiotics appear to be promising therapy for tuberculosis. Currently, there are many lung-microbiome-directed therapies are proposed for many diseases, but further studies should be made to determine the efficacy towards the host's health and safety. Therefore, though dietary supplements like prebiotics, postbiotics or probiotics can significantly alter the gut-lung axis limited evidence of the clinical improvement of lower respiratory conditions is available.

Future Directions/ Challenges and Conclusion

Studies suggest that alterations in the gut microbiota contributing to some positive responses towards TB infection are still emerging. However, future studies should focus on giving a clear understanding regarding whether any specific gut microbiome has an impact on TB susceptibility and the immune responses involved in TB pathogenesis. They should ensure that metabolomics characterises the peripheral blood metabolites produced by the host microbiome and must analyse their impact on various stages of TB disease. Since anti-tuberculous drugs have a great impact on the susceptibility of TB recurrence, studies should investigate the microbiome dysbiosis and the effect on TB re-infection and immune pathways. Experimental models should be done to explore whether probiotics, prebiotics and postbiotics can combat host dysbiosis when combined with anti-tuberculous drugs.

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