# Features of the etiopathogenesis of lung lesions in tuberculosis

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**Abstract:** Having a history of pulmonary tuberculosis (TB) is a risk factor for long-term respiratory failure. Post-tuberculous lung dysfunction often remains unrecognized, despite its relatively high prevalence and association with reduced quality of life. Importantly, the specific host and pathogen factors that cause lung injury remain unclear. The host immune response probably plays a major role in the lungs injury, as excessive inflammation and overexpression of lung matrix degrading proteases are common in tuberculosis. Variation in host genes that modulate these immune responses may determine the severity of lung injury, but this hypothesis remains largely untested.

**Keywords:** pulmonary tuberculosis, pulmonary insufficiency

One third of the world's population is infected with Mycobacterium tuberculosis (MTB), and more than 9 million new cases of tuberculosis (TB) are registered annually [1]. Treatment of drug-susceptible pulmonary tuberculosis is highly effective: an estimated 85% (66 million cases) of reported cases were successfully treated between 1995 and 2020year [1]. However, up to half of TB survivors have some form of a form of persistent pulmonary dysfunction despite microbiological treatment [2,5]. Pulmonary dysfunction, ranging from mild abnormalities to severe dyspnea, may increase the risk of death from respiratory causes [6,9]. Moreover, treated TB patients appear to be a significant contributor to the growing worldwide burden of chronic obstructive pulmonary disease (COPD) [10,12]. These findings call for the development of strategies to eliminate pulmonary insufficiency after TB (PIAT). A notable feature of lung involvement in tuberculosis is its striking heterogeneity. This is seen in formal lung function testing in terms of lung function magnitude, inranging from no impairment to severe dysfunction [3,7,8] and certain types of ventilation defects [3,11]. Patients may have cavitation, fibrosis or nodular infiltrates or a combination of these pulmonary pathologies [14]. This enormous variability may be due to host-pathogen interactions and the various immunological events that may follow. We also hypothesize that the heterogeneity of lung injury may be due in part to variations in genes encoding or regulating the host's immune response. Understanding the immune pathways and genetic risk factors for lung injury associated with TB may help develop treatments that specifically target the

immunological factors responsible for lung injury. Epidemiology. Initial studies among untreated or incompletely treated TB patients showed that lung disability was relatively frequent outcome [16, 17]. Since then, many studies have reported lung involvement after completion of TB treatment [5, 7, 8, 18] with persistence of defects for several years after treatment (Table 2) [2, 4, 13]. For example, in a South African study, airway obstruction was observed in 68% of patients with a history of TB treated up to 16 years (median 5.6 years) prior to assessment [13]. Although longitudinal studies have shown improvement in lung function with TB treatment, a significant proportion of patients have irreversible and often progressive lung defects [3, 4, 7, 8, 20]. In a prospective study of 74 hospitalized patients with newly diagnosed tuberculosis, 54% of them improved their lung function during treatment, while the rest either had no changes or worsened lung function [3]. Even in outpatient settings, where patients are presumed to be healthier than hospitalized patients, between a quarter [7] and one third [8] of patients had moderate or severe airway limitation at the end of treatment. A growing number of population-based studies have demonstrated that a history of TB increases the risk of airway obstruction and COPD [10]. A study of 14,050 patients from 18 countries showed that a history of TB increased the risk of obstructive airway disease by 2.5 times, independent of smoking and other clinical factors [10]. Another study (n=5571) showed a higher prevalence of COPD in people with a history of TB (30.7%) compared to people without TB (13.9%) [12]. In a large study of 13,522 adults aged ≥40 years in South Korea, history of tuberculosis and lesions on chest radiographs were associated with a 4.47-fold increase in airway obstruction (95% CI 3.07–6.51) after adjusting for age, smoking, and body type. mass index (BMI) and other confounding factors [15]. In addition, a meta-analysis demonstrated that history of TB treatment was a risk factor for COPD (pooled OR 3.05, 95% CI 2.42–3.85) independent of smoking and age [11]. Symptoms associated with airway obstruction include shortness of breath, decreased exercise tolerance, and chronic bronchitis [4]. The magnitude of airway obstruction is usually determined by measuring forced expiratory volume in 1 second (FEV1). FEV1 is reported both in absolute volume and as a percentage of predicted normal, with a decrease in FEV1 per 100 ml considered clinically significant. Several studies have observed a decrease in FEV1 during and after TB treatment [3, 7, 8, 11, 13]. A Korean study showed a mean decrease in FEV1 of 38.2±8 ml yr-1 [2] in cured TB patients, consistent with the rate of decline in FEV1 over time (33±2 ml yr-1) in COPD patients without TB [20]. A comparable rate of decrease in FEV1 was observed in a study that compared patients with a history of tuberculosis and a control group of the same age [4]. In addition, a study in Indonesia (n = 200) found moderate to severe airway obstruction (FEV 1 <60% to) in about half of patients at baseline and found only a slight improvement in % FEV 1 of 14.8% with treatment.

Restrictive ventilation defects Patients also suffer from restricted airflow [3, 13], the symptoms of which usually include chest pain, cough, and shortness of breath. Limitation is defined as a decrease in forced vital capacity lungs and/or an increase in the ratio of FEV1 / forced vitallung capacity [3]. In one study, restriction was found at the start and end of TB treatment in 57% and 24% of patients, respectively; but no further longitudinal analysis was performed in this study [3]. Although airway obstruction in tuberculosis is given the most Attention, mixed patterns of airway obstruction/restrictive ventilation defects were the most common form of pulmonary dysfunction in a review of population-based and observational studies conducted in South Africa [8]. Structural changes in the lung resulting from aberrant lung tissue repair [9] may explain airflow limitation in TB patients.Mediators of lung damage and dysfunction in tuberculosis. Targeted treatment of lung lesions in tuberculosis requires knowledge of the exact mechanisms of immune pathology. A major barrier to longitudinal study of the immunopathogenesis of tuberculosis in humans is that it is virtually impossible to obtain serial lung biopsies during disease progression and treatment that can be used to identify local immune pathways involved in tissue damage. Thus, our current understanding of the immunological underpinnings of lung tissue injury in TB is largely based on animal models. Although TB in non-human primates and some aspects of the disease in other animal models are similar to human diseases [5, 6], no single model captures the full spectrum of human lung pathology [14]. For example, a recent longitudinal study using positron emission tomography and CT to evaluate localized lung inflammation in patients with pulmonary TB found that many patients experience exacerbation and/or development of new inflammatory lesions despite 6 months of anti-TB therapy and after completion of 1 year of treatment. . Moreover, culture-negative patients at the end of treatment were found to have MTB mRNA in respiratory fluids, suggesting that persistent bacterial transcription may promote inflammatory responses in the lungs.

Immune mediators of tissue remodeling and impaired lung function in tuberculosis. Transcription factors, cytokines and chemokines that control the expression of tissue-degrading enzymes or directly mediate cavitation and/or fibrosis are shown in green. Matrix metalloproteinases (MMPs) that promote granuloma formation and cavitation are shown in purple. HIF: hypoxia inducible factor; NF: nuclear factor; IL: interleukin; TNF: tumor necrosis factor; TGF: transforming growth factor; IFN: interferon; mtROS: mitochondrial reactive oxygen species. IL-1β regulates fibrogenesis in idiopathic pulmonary fibrosis and may play a role in tuberculosis. Pathological processes that contribute to the progression of lesions may influence the development of airway obstruction and restrictive ventilatory patterns of lung failure. We also hypothesize that although certain immunological mechanisms may specifically cause airway obstruction or restrictive ventilatory

failure in TB, many patients may have significant overlap. Immune mediators and pathways that possibly cause necrosis and cavity formation during tuberculosis may also contribute to subsequent fibrosis. These immunological factors could potentially be targetedare aimed at preventing airway obstruction and/or restrictive ventilation defects after tuberculosis. Genetic predisposition to lung damage in tuberculosis. Epidemiological and immunological studies point to striking heterogeneity in inflammation, pulmonary pathology, and pulmonary functions in patients with tuberculosis. Although environmental factors such as smoking or exposure to silica among miners [7], differences in MTB virulence [14] or HIV coinfection [8] may contribute to this heterogeneity, variations in host genes that regulate the immune response to MTB may also be involved. The underlying mechanism lung damage in MMP-1 1G carriers remains unclear because it is the MMP-1 2G allele that introduces the Ets transcription binding site and increases MMP-1 expression [7]. According to the functional roleof the MMP-1 2G variant, a study showed that in patients with the MMP-1 2G/2G genotype, the risk of irreversible lesions after tuberculosis treatment was 6.5 times higher than in patients with other genotypes in this locus [14]. However, this association was only in the presence of an additional variant in the monocyte chemoattractant protein (MCP)-1 (MCP-1) promoter. Patients with MCP-1 G/G and MMP-1 2G/2G genotypes had extensive fibrosis and an increased prevalence of bronchiectasis at the end of TB treatment [6]. Thesestudies, however, did not assess lung function in relation to genotype andlung pathology.

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