Tuberculosis and lung damage: from epidemiology to pathophysiology

Shruthi Ravimohan[1], Hardy Kornfeld[2], Drew Weissman[1] and Gregory P. Bisson[1,3]

Affiliations: [1]Dept of Medicine, Division of Infectious Diseases, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. [2]Dept of Medicine, University of Massachusetts Medical School, Worcester, MA, USA. [3]Dept of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.

Correspondence: Shruthi Ravimohan, Dept of Medicine, Division of Infectious Diseases, University of Pennsylvania, 423 Guardian Drive, 930 Blockley Hall, Philadelphia, PA, USA.
E-mail: shruthir@pennmedicine.upenn.edu

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ABSTRACT A past history of pulmonary tuberculosis (TB) is a risk factor for long-term respiratory impairment. Post-TB lung dysfunction often goes unrecognised, despite its relatively high prevalence and its association with reduced quality of life. Importantly, specific host and pathogen factors causing lung impairment remain unclear. Host immune responses probably play a dominant role in lung damage, as excessive inflammation and elevated expression of lung matrix-degrading proteases are common during TB. Variability in host genes that modulate these immune responses may determine the severity of lung impairment, but this hypothesis remains largely untested. In this review, we provide an overview of the epidemiological literature on post-TB lung impairment and link it to data on the pathogenesis of lung injury from the perspective of dysregulated immune responses and immunogenetics.

Introduction

A third of the world's population is infected with *Mycobacterium tuberculosis* (MTB), and over 9 million new cases of tuberculosis (TB) are reported annually [1]. Treatment of drug-susceptible pulmonary TB is highly effective, with 85% (66 million cases) of reported cases estimated to have been successfully treated between 1995 and 2015 [1]. However, up to half of TB survivors have some form of persistent pulmonary dysfunction despite microbiologic cure [2–5]. Pulmonary dysfunction, ranging from minor abnormalities to severe breathlessness, can increase the risk of death from respiratory causes [6–9]. Furthermore, treated TB patients appear to contribute substantially to the growing worldwide burden of chronic obstructive pulmonary disease (COPD) [10–12]. These findings call for strategies to address pulmonary impairment after TB (PIAT).

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A notable feature of lung involvement in TB is its striking heterogeneity. This is observed on formal lung function testing in terms of the magnitude of pulmonary function, ranging from no impairment to severe dysfunction [3, 7, 8] and the specific types of ventilatory defects [3, 11, 13]. Patients may present with cavitation, fibrosis or nodular infiltrates, or have a mix of these pulmonary pathologies [14, 15]. This immense variability may relate to host–pathogen interactions and the diverse immunological events that can follow. We also hypothesise that heterogeneity in lung damage may be partially attributed to variation in genes coding for or regulating host immune responses. Elucidating the immune pathways and genetic risk factors for TB-associated lung injury could inform therapies that specifically target immunological factors responsible for lung injury.

This review summarises the epidemiology of PIAT, examines TB-associated lung pathology potentially linked to lung dysfunction, and reviews the immunological and plausible genetic correlates of lung tissue damage in TB. We also describe several processes, such as pulmonary cavitation, fibrosis and bronchiectasis, which probably contribute collectively to lung remodelling in TB and PIAT. These terms are defined in table 1.

Search strategy

For this review we identified references in PubMed that were published up to May 2017. We specifically searched for studies describing the epidemiology of impaired lung function post-TB treatment using the search terms "epidemiology", "pulmonary tuberculosis", "pulmonary function", "obstruction AND/OR restrictive", "bronchiectasis", "fibrosis", "cavitation" and "TB treatment". For studies on lung pathology and mediators of inflammation in TB we used the terms "pulmonary tuberculosis", "lung pathology", "immunopathology", "matrix metalloproteinase", "inflammatory biomarkers OR inflammation", "neutrophils" and "CD4 T cells". Genetic studies were queried using the terms "pulmonary tuberculosis", "genetics", "COPD" and "idiopathic pulmonary fibrosis". Relevant articles published in English that resulted from the searches, and references cited therein, were reviewed.

PIAT

Epidemiology

Initial studies conducted among untreated or incompletely treated TB patients highlighted that lung disability was a relatively common outcome [16, 17]. Many studies since have reported on lung impairment at TB treatment completion [5, 7, 8, 18], with persistence of defects several years post cure (table 2) [2, 4, 13]. For example, a South African study observed airflow obstruction in 68% of patients with a history of TB treated up to 16 years (mean 5.6 years) prior to assessment [13]. Although longitudinal studies have shown improvement in pulmonary function with TB treatment, a considerable proportion of patients have irreversible and often progressive pulmonary defects [3, 4, 7, 8, 20]. In a prospective study of 74 hospitalised patients with newly diagnosed TB, 54% had improved lung function with treatment and the rest had either no change or worsening pulmonary function [3]. Even in the

TABLE 1 Definitions for processes contributing to lung remodelling during pulmonary tuberculosis (TB) and pulmonary impairment after TB

Term	Definition
Pulmonary cavitation	Process by which normal pulmonary tissue is obliterated, becoming gas-filled spaces or cavities in the lung. This process initially involves caseous necrosis of lipid pneumonia lesions, producing caseous pneumonia. During caseation, alveolar cells and septa are destroyed along with neighbouring vessels and bronchi. Cavities form when these regions of caseous pneumonia liquefy, fragment and are released upon coughing.
Pulmonary fibrosis	Results from long-term lung tissue injury that is characterised by excessive extracellular matrix deposition in the lung. Replacement of normal lung parenchyma with collagenous tissue results in architectural changes in the lung, such as thickening and stiffening of the lung walls.
Bronchiectasis	Manifests as irreversible bronchial dilatation and thickening of the bronchial wall. Elastic and muscular components of the bronchial wall are destroyed in bronchiectasis. Bronchial dilatation associated with bronchiectasis in TB may be due to multiple factors, including traction from surrounding tissue fibrosis, caseous necrosis that makes its way into the bronchi, and elevated luminal pressure due to coughing. Bronchiectasis can also predispose to recurrent exacerbations of purulent sputum production and possibly bacterial pneumonia in subsequent years.
Pulmonary impairment after TB	A broad term we use in this review to refer to lung dysfunction that includes airflow obstruction, restrictive ventilatory defects and impaired gas exchange. Pulmonary impairment after TB is probably downstream of a wide variety of lung remodelling events, some of which are described above. Given the lung's considerable reserve, these structural changes may manifest as symptoms and pulmonary disability over a period of time.

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TABLE 2 Summary of epidemiological studies investigating pulmonary impairment after tuberculosis (TB)

First author [ref.]	Type of study	Setting	Sample size n	Exposure	Outcome	Association/finding	Major limitation
Akkara [18]	Cross-sectional	India	257	Treated TB (2 weeks post-treatment completion)	Airflow obstruction measured by FEV_1 and FVC	Airflow obstruction in 86.8% of patients	Lung impairment before TB treatment initiation was not measured to relate to lung impairment after treatment completion and determine causality. Long-term lung disability was not assessed.#
Willcox [13]	Cross-sectional	South Africa	71	History of TB (up to age 16 years)	Airflow obstruction defined as RV >120% pred and/or FEV_1/FVC ratio <70% pred with TLC >80% of pred	Obstruction in 68% of patients Obstruction with some restriction in 20% Non-obstructive decrease in lung volume in 17%	Lung impairment before TB treatment initiation was not measured to relate to lung impairment after treatment completion and determine causality. Lung function was evaluated only in patients who could be traced after several years of attending a TB clinic. Selection of patients in this way may have contributed to survivor bias and underestimated lung dysfunction.
Manji [19]	Cross-sectional	Tanzania	501	Treated TB (20 weeks of anti-TB therapy)	Airflow defects measured by FEV_1 and FVC	Lung impairment in 74% of patients Obstruction in 42% Restriction in 13% Mixed pattern in 19%	Lung impairment before TB treatment initiation was not measured to relate to lung impairment after treatment completion and determine causality. Long-term lung disability was not assessed.#
Hnizdo [2]	Retrospective	South Africa	27 660	History of 1, 2 or ⩾3 episodes of TB	Airflow obstruction defined as FEV_1 <80%	Prevalence of airflow obstruction after 1 episode of TB (18.4%), 2 episodes of TB (27.1%) and ⩾3 episodes of TB (35.2%) Lung impairment is greatest in the first 6 months following TB diagnosis and stabilises 6 months post-TB treatment completion	Only male mine workers were assessed.

Continued

TABLE 2 Continued

First author [ref.]	Type of study	Setting	Sample size n	Exposure	Outcome	Association/finding	Major limitation
Ross [4]	Matched retrospective	South Africa	185 TB cases *versus* 185 age-matched controls without history of TB	History of TB	Lung function loss over time measured by FEV_1 and FVC	History of TB was associated with an adjusted mean loss of 40.3 mL·year^{-1} in FEV_1 (95% CI 25.4–55.1) and 42.7 mL·year^{-1} in FVC (95% CI 27–58.5) compared to controls	Only male mine workers were assessed. Patients were included in the study only if they were still working in the mines at follow-up, nearly 4.5 years after baseline measures. Several subjects had left the mines by follow-up. Selecting only those still working at the mines may have contributed to survivor bias and underestimated lung function.
Rhee [20]	Retrospective	Republic of Korea	595	Destroyed lung resulting from a past history of TB	Lung function loss measured by FEV_1 and FVC	Lung impairment after TB in 76.8% of patients	Cohort consisted of hospitalised TB patients with destroyed lungs, thereby limiting the generalisability of findings to less advanced patients. PFTs were not standardised.
Plit [3]	Prospective cohort	South Africa	74	TB treatment	Lung function at the end of TB treatment	54% of patients had an improvement in lung function 28% of patients had obstructed airflow 24% of patients had restricted airflow Only study to date that has investigated an association between inflammation and lung function: elevated C-reactive protein correlated with decreased FEV_1 % after TB treatment completion, independent of smoking	Cohort consisted of hospitalised patients with severe TB, thereby limiting the generalisability of findings to less advanced patients. Long-term lung disability was not assessed.[#]

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TABLE 2 Continued

First author [ref.]	Type of study	Setting	Sample size n	Exposure	Outcome	Association/finding	Major limitation
Maguire [7]	Prospective cohort	Indonesia	69	TB treatment	Lung function over the course of TB treatment	Lung function improved over the course of TB treatment; however, 25% of the patients had residual moderate-to-severe TB (FEV_1 <60%) at treatment completion	Study was restricted to 69 of 115 patients who attended all follow-up visits. Those included were more likely to have been cured and had better lung function at diagnosis compared to those not included. This may have underestimated the extent of lung dysfunction among patients with a history of TB. Long-term lung disability was not assessed.[#]
Ralph [8]	Prospective cohort	Indonesia	200	TB treatment	Lung function over the course of treatment and at treatment completion	47% of TB patients had moderate-to-severe pulmonary impairment at baseline 27% of TB patients had residual moderate-to-severe pulmonary impairment at the end of treatment	Long-term lung disability was not assessed.[#]
Pasipanodya [5]	Case–control	USA	107 active TB cases *versus* 210 latent TB controls	Treated TB (20 weeks of anti-TB therapy)	Airway obstruction defined as FEV_1/FVC <70% pred and FVC >80% pred	TB patients on anti-TB therapy have significantly higher odds of pulmonary impairment *versus* controls with latent TB, OR 5.4 (95% CI 2.98–9.68)	Lung impairment before TB treatment initiation was not measured to relate to lung impairment at treatment completion and determine causality. Long-term lung disability was not assessed.[#]
Amaral [10]	Cross-sectional, population-based study of adults	18 high and low-/ middle-income countries	14 050	History of TB	Airflow defects: obstruction defined as post-bronchodilator FEV_1/ FVC less than LLN; restriction defined as post-bronchodilator FVC less than LLN	Obstruction: adjusted OR 2.51 (95% CI 1.8–3.42) Restriction: adjusted OR 2.31 (95% CI 1.42–3.19)	Self-report of TB was used to determine association with airflow obstruction. This approach may have resulted in recall bias.

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TABLE 2 Continued

First author [ref.]	Type of study	Setting	Sample size n	Exposure	Outcome	Association/finding	Major limitation
Menezes [12]	Cross-sectional, population-based	5 Latin American cities	5571 patients; 132 with a diagnosis of TB	History of TB	COPD	Prevalence of COPD in 30.7% *versus* 13.9% comparing those with and without history of TB, respectively Smoking adjusted OR 2.33 (95% CI 1.5–3.62)	History of TB was not confirmed by medical records. Lung function was not measured
Lee [21]	Retrospective	Taiwan	3176 pulmonary TB cases *versus* 15 880 matched controls	History of TB	COPD	History of TB is an independent risk factor of COPD (HR 2.05, 95% CI 1.77–2.39)	Patients were considered to have a history of TB and COPD based on medical treatment records. Lung function was not measured.
Byrne [11]	Systematic review and meta-analysis	Multiples countries		History of TB	COPD	History of TB was significantly associated with COPD in adults over 40 years (pooled OR 3.05, 95% CI 2.42–3.85)	All studies included in the meta-analysis were cross-sectional. Thus, precluding determination of a temporal and causal effect of TB on COPD.

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; PFT: pulmonary function test; LLN: lower limit of normal; COPD: chronic obstructive pulmonary disease. #: the study by Hnizdo *et al.* [2] demonstrated that lung impairment peaks 6 months after diagnosis, but improves 6 months post-treatment completion before stabilising to become chronic. These studies determined lung function at treatment completion, thus their findings may not represent residual lung impairment.

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outpatient setting, where patients are presumably healthier than those who are hospitalised, a quarter [7] to one-third [8] of the patients had moderate-to-severe airway limitation at treatment completion. Other groups have corroborated these findings in multiple other settings [5, 19, 22, 23]. A limitation of many of the studies described above, however, was their small-to-moderate sample size (study-specific limitations are described in table 2).

An increasing number of population-based studies have demonstrated that a history of TB increases risk for airflow obstruction and COPD [10–12, 22]. A study of 14050 patients from 18 countries revealed that a history of TB increased risk for obstructive airway disease by 2.5-fold independent of smoking and other clinical factors [10]. Another study (n=5571) showed a higher prevalence of COPD in those with a history of TB (30.7%) *versus* those without (13.9%) [12]. In a large study of 13522 adults aged ⩾40 years set in South Korea, a history of TB and lesions on chest radiographs were associated with 4.47 increased odds of airflow obstruction (95% CI 3.07–6.51) after adjusting for age, smoking, body mass index (BMI) and other confounders [24]. Furthermore, a meta-analysis demonstrated that a history of treated TB was a risk factor for COPD (pooled OR 3.05, 95% CI 2.42–3.85) independent of smoking and age [11].

Risk factors associated with PIAT have not been fully elucidated and the relationships are probably complicated. It has been suggested that smoking, which is an established risk factor for COPD, may contribute to PIAT [2, 3, 5]. However, some reports have found no such association [4, 7, 8]. For example, in one study individuals with a history of TB were twice as likely to be current smokers than those in the non-TB group; yet, greater lung dysfunction over time in the TB group was independent of smoking in a multivariate analysis [4]. A similar lack of association between smoking and impaired lung function was observed among patients completing TB treatment in Indonesia [7, 8]. HIV co-infection may be an additional risk factor for lung function decline. Several studies have now shown that HIV-infected patients are at increased risk for impaired gas exchange as well as airway obstruction [25–27]. However, data are conflicting and sparse with respect to lung function in HIV/TB co-infected patients [2, 8]. Other risk factors for poor lung function after TB may include comorbidities such as diabetes, as well as environmental factors like indoor smoke from biomass fuels. Although these risks have been linked to COPD [26, 28], they remain to be investigated in the context of post-TB lung disability.

Variability in lung function deficits

PIAT can involve airflow obstruction and/or restrictive ventilatory defects, as well as impairment in gas exchange (figure 1) [3, 11, 13, 15, 20]. Airflow defects can be detected by spirometry, which quantitates the flow and volume of air inhaled and exhaled [29]. Impaired gas exchange is determined by measuring the diffusing capacity of the lung for carbon monoxide (*D*LCO) [30]. The American Thoracic Society and the European Respiratory Society provide standardised guidelines on conducting and

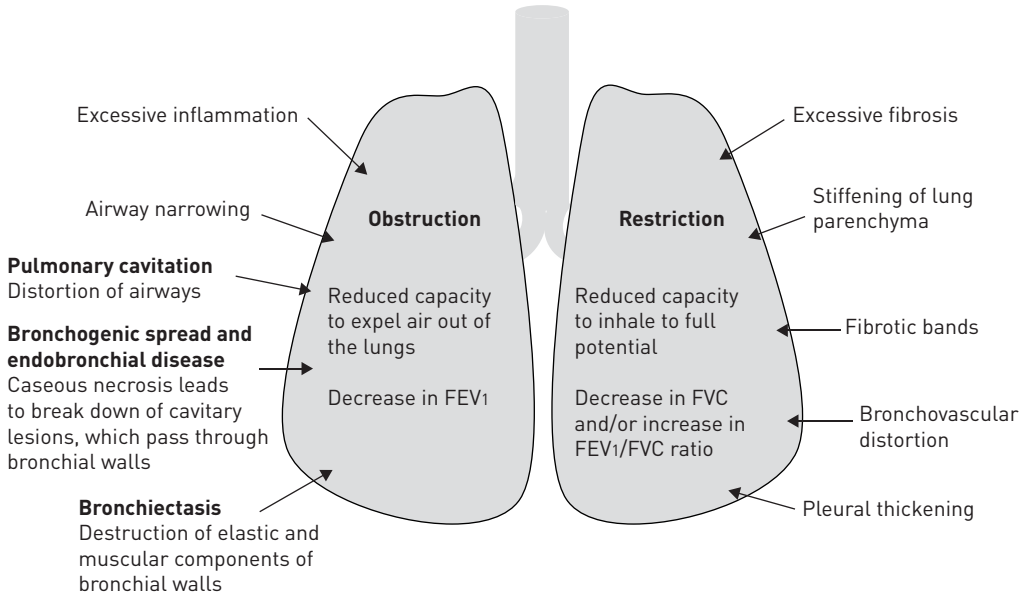

FIGURE 1 Mechanisms and radiographic features associated with airflow obstruction and restrictive ventilatory defects in patients with a history of tuberculosis. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.

interpreting these tests [30–32]. Airflow obstruction is associated with decreased capacity to completely expel air out of the lungs and is probably due to inflammation-induced narrowing of airways. In contrast, restriction is probably linked to the reduced ability to inhale fully resulting from extensive fibrosis and stiffening of the lung parenchyma. Lung manifestations of pneumonia are mediated, in part, by immune mechanisms [14, 33], and so heterogeneity in pulmonary deficits in TB may be linked to variability in the host's response to MTB.

Airflow obstruction

Symptoms associated with airflow obstruction include dyspnoea, reduced exercise capacity and chronic bronchitis [34]. The magnitude of airway obstruction is commonly quantified by measuring the forced expiratory volume in 1 s (FEV_1) [32]. FEV_1 is reported as both an absolute volume and as a percentage of predicted normal [32], with a 100 mL decrease in FEV_1 being considered clinically significant [35]. Several studies have observed a decline in FEV_1 during and after TB treatment [3, 7, 8, 11, 13, 20]. A Korean study found a mean FEV_1 decline of 38.2±8 $mL \cdot year^{-1}$ [20] in cured TB patients that was consistent with the rate of reduction in FEV_1 over time (33±2 $mL \cdot year^{-1}$) in COPD patients without TB [20]. Comparable rates of FEV_1 decline were observed in a study comparing patients with a history of TB to age-matched controls [4]. Additionally, a study in Indonesia (n=200) found moderate-to-severe (FEV_1 <60% pred) airflow obstruction in approximately half the patients at baseline and determined only a small improvement of 14.8% in % FEV_1 with treatment [8].

Decline in FEV_1 may be linked to multiple underlying pathological mechanisms (figure 1). Pulmonary cavitation may obliterate or distort airways, leading to airflow obstruction. In a study of serial changes in lung structure and pulmonary function, patients with cavities had significantly lower FEV_1 at baseline and at 1 month post-TB treatment initiation compared to patients without cavities [15]. Additionally, bronchogenic spread is a hallmark of pulmonary TB, where caseous material released during cavitary disintegration passes through the bronchial walls [14, 36–38]. Furthermore, destruction of elastic and muscular components of the bronchial walls resulting in bronchiectasis, which is associated with airflow obstruction [39], was detected more frequently in patients with cavities (64%) than those without (11%) [15]. Bronchiectasis is a permanent distortion of airways that predisposes to lifelong morbidity with recurrent episodes of purulent sputum production, haemoptysis and sometimes progression to pneumonia [40]. Bronchiectasis as a sequela of pulmonary TB has been long recognised [41] and can persist or worsen despite TB treatment completion [42]. *Post mortem* autopsy studies of TB patients found bronchiectasis in 19–65% of those examined [43, 44]. It is alarming to note that in one study, conducted more recently, 86% patients had cylindrical bronchiectasis 6 months post-TB treatment on chest computed tomography (CT) [45]. Consistently, a systematic review reported the prevalence of bronchiectasis post-TB to be 35–86% in the five CT studies they assessed [46]. Furthermore, a population-based study of >10 000 adults in China revealed that having a history of TB increased the odds of having a diagnosis of bronchiectasis three-fold compared to those without previous TB (OR 3.07, 95% CI 1.89–4.98) [47]. However, our understanding of the mechanisms that drive such structural changes and associated airflow obstruction following TB are poor.

Restrictive ventilatory defects

Patients also suffer from restricted airflow [3, 13, 18, 19], where symptoms commonly include chest pain, cough and shortness of breath. Restriction is defined either as a decrease in forced vital capacity and/or an increase in the FEV_1/forced vital capacity ratio [32]. In one study, restriction was detected at baseline and at the end of TB treatment in 57% and 24% of patients, respectively; however, further longitudinal analyses were not performed in this study [3]. Although airflow obstruction in TB has received the greatest attention, mixed patterns of airflow obstruction/restrictive ventilatory defects was the most common form of lung dysfunction in a review of population-based and observational studies conducted in South Africa [48]. Structural changes in the lung resulting from aberrant lung tissue repair (*e.g.* bronchovascular distortion, fibrotic bands and pleural thickening) [15, 20, 49] may explain airflow restriction in TB patients.

Impaired diffusing capacity and ventilation/perfusion mismatch

There is also evidence for impaired gas exchange early in TB disease [50, 51]. Decrease in D_{LCO} is probably due to reduction in surface area for gas exchange following alveolitis or "lipoid pneumonia", which occurs during cavitation (described in the Granulomas to cavitation during TB section). Although D_{LCO} improves with treatment, some individuals may have permanently impaired diffusion and ventilation/perfusion mismatch, resulting in chronic hypoxaemia [15, 52]. Long-term oxygen therapy is known to improve outcomes in COPD patients with severe chronic hypoxaemic respiratory failure [53, 54]. Currently there is little information on the prevalence of severe hypoxaemia in TB survivors.

Mediators of lung damage and dysfunction in TB

Targeted treatment of TB-associated lung impairment requires knowledge of the precise mechanisms of immune pathology. A major barrier to studying TB immunopathogenesis longitudinally in humans is that serial lung biopsies through disease progression and treatment, which could be used to determine local immune pathways involved in tissue injury, are nearly impossible to obtain. Thus, our current understanding of the immunological basis for lung tissue injury in TB derives largely from animal models. Although TB in non-human primates and certain aspects of disease in other animal models are similar to human disease [55, 56], no single model recapitulates the entire spectrum of human lung pathology [14]. Nevertheless, human studies and data from animal models provide compelling evidence for the crucial role of the host's immune response to MTB in lung remodelling (summarised in figure 2). Such host–pathogen interactions may persist even after treatment completion. For example, a recent longitudinal study using positron emission tomography and CT to evaluate local lung inflammation in pulmonary TB patients demonstrated that many patients have enhancement and/or development of new inflammatory lesions despite 6 months of anti-TB therapy and following 1 year of treatment completion [57]. Moreover, patients deemed culture negative at the end of treatment were found to have MTB mRNA in respiratory fluids, suggesting persistent bacterial transcription may fuel inflammatory reactions in the lung [57]. Although this study did not conduct formal lung function tests, patients had signs and symptoms consistent with lung impairment [57].

We also hypothesise that while certain immunological mechanisms may specifically drive TB-associated airflow obstruction or restrictive ventilatory impairment, many patients could have considerable overlap. Immune mediators and pathways that perhaps drive necrosis and cavitation during TB may also set up for subsequent fibrosis. These immunological factors could potentially be targeted to prevent airflow obstruction and/or restrictive ventilatory defects after TB.

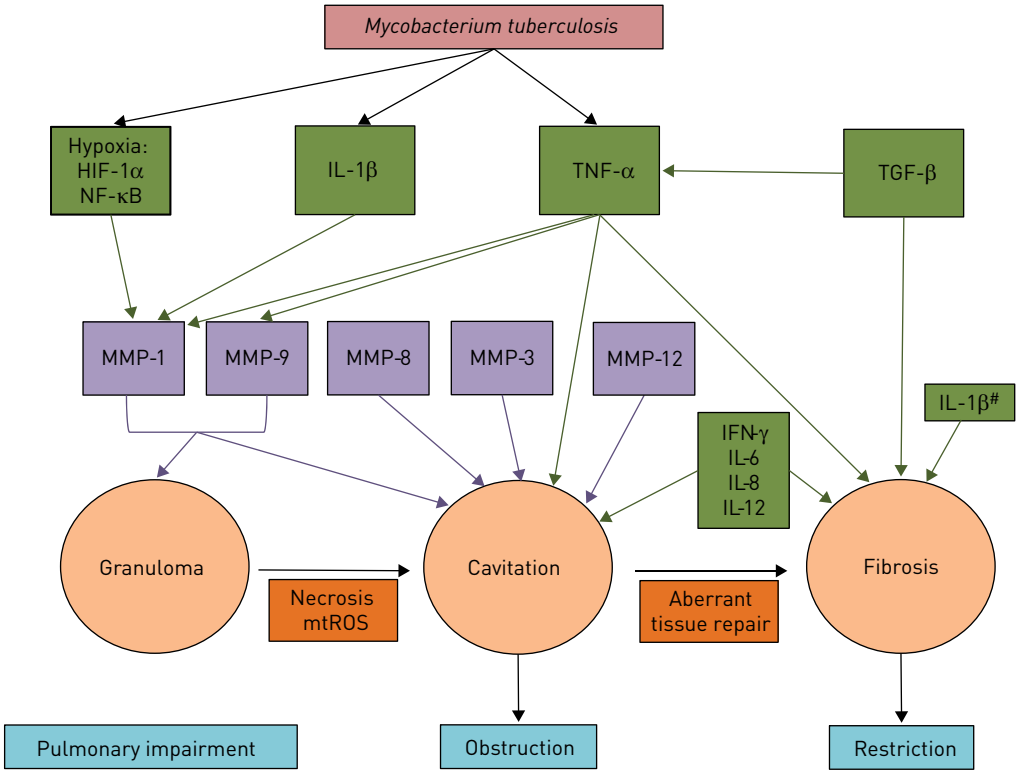

FIGURE 2 Immune mediators of tissue remodelling and lung function impairment in tuberculosis. Transcription factors, cytokines and chemokines that drive expression of tissue-degrading enzymes or directly mediate cavitation and/or fibrosis are shown in green. Matrix metalloproteinases (MMP) that promote granuloma and cavitation are depicted in purple. HIF: hypoxia inducible factor; NF: nuclear factor; IL: interleukin; TNF: tumour 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 contributing to the progression of lesions may influence the development of airflow obstruction and restrictive ventilatory patterns of pulmonary impairment.

Granulomas to cavitation during TB

The host's immune system responds to the invading mycobacterium and triggers granuloma formation during primary infection [14, 58]. A granuloma is a highly organised structure consisting of many immune cell types (*e.g.* macrophages, neutrophils, natural killer cells and T- and B-cells) that surround a caseous necrotic core of MTB-infected alveolar macrophages [33, 58]. The granuloma is traditionally thought to be host-protective by sequestering and preventing dissemination of MTB, but studies using the zebrafish model for TB have demonstrated that granulomas can be conducive to MTB proliferation and spread [59, 60]. Moreover, there appears to be substantial heterogeneity in the bacterial load, size and inflammatory profile between granulomatous lesions within a single host based on recent non-human primate studies [61–63]. It has been shown that a single or few granulomas that fail to control mycobacterial proliferation can dramatically influence disease progression and clinical outcome [64].

A widely held view, based on data from animal models, is that these granulomas coalesce and breakdown *via* liquefactive necrosis, leaving behind a cavity during active disease [56, 65]. However, human studies suggest that cavities originate from lipid pneumonia during post-primary TB [14, 66]. These lipid pneumonia lesions may develop into areas of caseous pneumonia as a result of caseous necrosis [14, 66]. During caseous necrosis, alveolar cells are destroyed, along with nearby structures such as vessels and bronchi [14]. However, elastic fibres of the alveolar walls and vessels appear to remain intact [14, 67]. This necrotic tissue begins to soften and fissure and is eventually coughed out [14, 67]. Gas-filled spaces surrounded by a collagen capsule in turn replace normal lung tissue following cavitation.

Although the precise immune mechanisms underlying liquefactive or caseous necrosis are not fully understood, robust immune responses probably play a significant role [68, 69]. Initial evidence for this comes from Robert Koch's observations over a century ago. He noted that when guinea pigs previously infected with MTB are rechallenged, they develop necrotic lesions that expand in circumference at the site of cutaneous injection [70]. The Koch Phenomenon has been described by others [71], including Moreira *et al.* [72], where MTB-infected mice were treated with a recombinant bacillus Calmette–Guerin (BCG) vaccine that released cytokines (*e.g.* tumour necrosis factor (TNF)-α) shown to reduce bacterial burden in a pre-infection vaccine model. Paradoxically, post-infection treatment with BCG–TNF-α exacerbated lung pathology without decreasing MTB load in these mice [72]. Furthermore, Shwartzman [73] found that rabbits previously injected with Gram-negative bacteria in the skin developed haemorrhagic necrosis at the initial site of injection following an intravenous injection of the same bacteria 24 h later. This reaction may be explained, in part, by T-cell mediated MTB-specific immune responses, given that depleting $CD4^+$ T-cells in pre-immunised mice inhibited this reaction [74]. This study also highlighted an important role for TNF-α in perpetuating necrosis [74]. Other studies have corroborated these findings [75]. In addition to an excessive and tissue-damaging immune response directed towards viable and nonviable mycobacteria [65, 76], dysregulation of host lipid metabolism has recently been hypothesised to influence caseous necrosis [77]. We expand our discussion on possible immune mechanisms underlying lung pathology and dysfunction in the sections below.

Regardless of the way granulomas and cavities form, they can have variable trajectories of resolution through the course of disease or treatment, and may undergo abnormal repair resulting in focal or extensive tissue fibrosis [14, 78]. Thus, it is plausible that host immune responses that drive inflammation, cavitation and fibrosis contribute to the variable patterns of lung healing, manifesting as persistent airflow obstruction and/or restrictive ventilatory defects. Additionally, differences in the quality and quantity of immune effector responses underlying these processes may also contribute to variability in PIAT.

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of 25 potent proteases that can degrade extracellular matrix components [79] and are probably central to TB-associated lung injury. MMPs can promote different stages of lung remodelling during TB [80]. Transcriptomic analyses of lesion biopsies from TB patients showed dramatic upregulation of tissue damaging networks that included *MMP-1* and *MMP-9* gene expression [81]. Furthermore, TB patients with chest radiographs showing extensive lung involvement had 8.5-fold higher levels of MMP-1 in their bronchoalveolar lavage (BAL) *versus* patients with less lung involvement [82]. Consistent with this, transgenic mice expressing human MMP-1 had greater alveolar wall damage and matrix destruction following MTB infection *versus* wild-type mice [82]. A recent imaging study revealed that TB lesions in humans are severely hypoxic [83]. Reproducing hypoxia in *in vitro* culture conditions resulted in upregulation of MMP-1 in MTB-infected cells *via* hypoxia-inducible factor and nuclear factor (NF)-κB activation [83]. Collectively, these studies suggest an important role for MMP-1 in lesion progression during TB that plausibly occurs upstream of lung impairment.

MMPs are tightly regulated at the level of transcription and proteolytic maturation, as well as by tissue inhibitors of metalloproteinases (TIMPs) [84]. In a rabbit model for cavitary TB disease, MTB was shown to drive an imbalance in MMP-1 and its specific inhibitor, TIMP-3, which associated with the progression of consolidated regions in the lungs to cavities [85]. Also, dysregulation in MMPs/TIMPs was demonstrated in the plasma [84] and respiratory fluids [82] of patients with active TB. Thus, uninhibited MMP expression and activity may lead to tissue destruction that ultimately contributes to PIAT.

Multiple other MMPs have been implicated in perpetuating TB-associated lung injury. For example, neutrophil-derived MMP-8 and -9 were associated with cavitary disease in TB patients [86]. In a pilot study of advanced HIV/TB co-infected patients, rapid increase in MMP-8 levels following antiretroviral therapy (ART) initiation was associated with impaired lung function nearly 2 years after TB treatment completion [87]. These preliminary findings are in line with the tissue destructive role of MMP-8 [87]. MMP-3 [82] and -12 [88] may also induce lung injury during TB. Although TB treatment appears to decrease sputum MMP-1, -3 and -8, they do return to normal levels [89]. Several other proteases such as neutrophil-associated elastase, proteinase-3 and cathepsin G have also been linked to matrix degradation in COPD and may participate in destroying lung tissue during TB [90]. Taken together, it is conceivable that a complex network of MMPs and other proteases mediate TB-associated lung injury with long-term impact on lung function.

Inflammatory cytokines

Few studies have directly investigated the relationship between inflammation and lung function in TB. A study by Plit *et al.* [3] demonstrated that elevated C-reactive protein, which is a non-specific inflammatory marker, correlated with decreased FEV_1 in TB patients after treatment completion. In clinical trials of adjunctive corticosteroid *versus* standard therapy alone for TB [91–93], lung disability was generally the same between groups; however, steroid administration increased vital capacity in one report [93]. It should be noted that adjunctive steroid treatment in TB patients has been associated overall with a trend towards improved clinical outcome [94–96], but its prolonged use at higher doses should be approached with caution given the long-term cardiovascular and metabolic risks. Furthermore, corticosteroids broadly suppress inflammation by inhibiting NF-κB signalling [97, 98], which regulates the expression of several cytokines including interleukin (IL)-1, IL-2, IL-6, IL-8, TNF-α and interferon (IFN)-γ. Thus, preventing or treating TB-associated lung impairment may require a more targeted approach.

TNF-α is a key regulator of host immune responses to TB with pleiotropic effects [99]. Intracellular pathogen clearance *via* macrophage activation is a crucial host-protective role of TNF-α [99, 100]. This cytokine can also promote apoptosis [101]. Apoptosis is a non-inflammatory mode of cell death that eliminates infected cells; however, TNF-α-induced apoptosis appears suboptimal for MTB control [100]. Moreover, MTB can stimulate expression of an inhibitor of TNF-α, soluble TNF-receptor II (sTNF-RII), and evade apoptosis [102]. Low levels of TNF-α may be problematic, as this has been shown to lead to inefficient macrophage activation and reduced microbicidal activity [103]. With uninhibited MTB replication, excessive inflammation and necrosis can ensue [103]. Conversely, elevated TNF-α levels may drive necrosis through the induction of mitochondrial reactive oxygen species, despite reduced MTB growth [103, 104]. The hyper-inflammatory nature of necrotic cell death can ultimately cause cavitation and lung tissue damage. Of note, a higher ratio of TNF-α to sTNF-RI and -RII correlated with larger cavity size [105]. Moreover, TNF-α is necessary for MMP-1 and -9 expression by monocyte–bronchial epithelial cell networks [106, 107]. Taken together, TNF-α perhaps potentiates tissue destruction in multiple ways during TB.

In addition to TNF-α, elevated IL-6, IL-8 and IL-12 levels in the BAL have been correlated with cavities, bronchial wall thickening and fibrotic bands in active TB patients [108]. In another pulmonary TB study, several cytokines were compared between patients classified as early or late responders based on improvement in chest radiographs after 2 or 6 months of TB treatment, respectively [109]. Late responders had higher levels of IL-1β, TNF-α and IFN-γ *versus* early responders [109], implicating these cytokines in lung tissue injury. Notably, TNF-α levels can rapidly increase following TB treatment [110]. Given that inflammatory cytokines levels are highly dynamic soon after TB treatment initiation [89, 111], lung remodelling is perhaps ongoing during and after TB treatment completion.

Fibrogenic cytokines

Permanent changes in lung architecture after TB may be, in part, due to aberrant wound-healing processes. Excessive collagen deposition and fibrotic scarring can occur through the course of TB disease and treatment [14, 112]. TNF-α may play a role in tissue fibrosis after TB. Treatment of MTB-infected rabbits with etanercept, a TNF-α antagonist, reduced expression of several genes involved in fibrosis and collagen metabolism [113]. Transforming growth factor (TGF)-β is considered the principal mediator of

fibrogenesis [114]. Activation of the TGF-β signalling pathway correlated with elevated collagen levels in lung lesions before and during TB treatment [112]. In pleural TB patients, higher TGF-β levels in the pleural fluid associated with greater pleural thickening before and after anti-TB therapy [49]. Additionally, IL-1β has been linked to fibrosis in patients with idiopathic pulmonary fibrosis (IPF), which is a progressive and fatal lung disease characterised by restrictive ventilatory defects [115]. Specifically, an imbalance in IL-1β and its receptor antagonist (IL-1RA) was implicated in propagating a pro-fibrotic milieu in IPF [116]. TB patients were reported to have a similar imbalance in IL-1β and IL-1RA that correlated with enhanced cavity size [105]. Although this study did not evaluate the relationship between IL-1β/IL-1RA imbalance and fibrosis [105], it is plausible that such dysregulation may contribute to aberrant tissue repair in TB patients. Collectively, TNF-α, TGF-β and IL-1β mediated fibrogenesis may contribute to restrictive ventilatory defects in patients with a history of TB and requires further investigation.

Neutrophils and CD4 T-cells

Multiple cell types have been implicated in orchestrating the development and progression of lesions and ultimately lung damage in TB. During primary infection, the first cell type infected with MTB is thought to be the lung-resident alveolar macrophage [14, 117]. These cells release inflammatory cytokines and chemokines upon activation, in turn recruiting both innate (natural killer cells, neutrophils, γ/δ T-cells and dendritic cells) and adaptive immune cells to the site of infection [65, 118]. While these early events are essential for containing the pathogen, dysregulation of immune responses probably drive caseation and cavitation [58, 119]. Evaluating the contribution of each of these cell types in TB-associated lung damage is beyond the scope of this review; however, we will discuss the role of neutrophils and $CD4^+$ T-cells in mediating tissue injury during TB disease.

Studies using murine models of TB have attributed a protective role for neutrophils very early in infection; however, these cells appear to play an adverse role during chronic, poorly controlled TB disease [120–122]. For example, MTB-infected neutrophils were found to facilitate host-protective adaptive immune response by delivering TB antigens to dendritic cells shortly after infection in mice [121]. Depletion of neutrophils led to decreased migration of dendritic cells to lymph nodes, as well as delayed activation and reduced proliferation of naïve TB-specific CD4 T-cells in these mice [121]. In contrast, massive infiltration and accumulation of neutrophils in the lungs is associated with increased pathology later in disease [123–125]. Consistently, depletion of neutrophils reduced lung injury in a hyper-susceptible mouse model of TB [126].

In humans, neutrophils are perhaps the predominant cell type in the lungs that are infected with replicating MTB during active pulmonary TB [127]. Moreover, it has been reported that cavitary lesions in humans are primarily lined by neutrophils [86, 127]. Several different tissue-damaging pathways may be triggered by neutrophils. In one study that examined lung biopsies, the cavity walls stained positive for neutrophils expressing extracellular matrix destroying MMP-8 and -9 [86]. Another study demonstrated that lung pathology resulting from neutrophilic inflammation during TB was dependent on calprotectin (S100A8/A9) secretion by these cells [122]. S100A8/A9 may not only be a surrogate for lung inflammation, but may also stimulate influx of destructive neutrophils to the lungs [122], along with other chemokines such as CXCL5 [128].

There is a growing body of evidence for the induction of neutrophil extracellular traps in TB [129, 130], which could fuel tissue damage and pulmonary dysfunction as observed in other lung diseases [131–133]. Neutrophil extracellular traps are released upon neutrophil activation and function to capture and kill bacteria [134]. They are composed of chromatin fibres, histones and proteases such as myeloperoxidase (MPO), capthesin G and neutrophil-associated elastase [134, 135]. Although these proteases have antimicrobial properties, they can potentially drive severe lung pathology [136–138]. Of note, MMP-8 and calprotectin have recently been found within neutrophil extracellular traps [86, 139]. Collectively, these studies underscore the contribution of inflammatory neutrophils in driving lung injury.

CD4 T-cells mount protective TB-specific responses; however, these cells may perpetuate tissue damage if their responses go unchecked [87, 140]. The association between CD4 T-cells and lung damage is evident from studies of advanced HIV/TB co-infected patients. In one study, HIV/TB patients with CD4 counts $<150\ \text{cells}\cdot\mu L^{-1}$ were five times more likely to have a normal chest radiograph than HIV-negative TB patients [141]. Moreover, ART-mediated reversal of CD4 lymphopenia in advanced HIV/TB patients is associated with incident lung involvement, particularly in those who experience TB-immune reconstitution inflammatory syndrome (IRIS) [142]. In a small study, TB-IRIS and robust CD4 T-cell recovery after ART initiation were associated with lower FEV_1 post-TB treatment completion [87]. Mechanistically, TB-specific CD4 T-cells that secrete TNF-α and IFN-γ perhaps trigger multiple downstream pathways and the activation of effectors like MMPs. These responses may converge on excessive inflammation and tissue injury and subsequent lung disability.

Genetic predisposition for lung injury in TB

Epidemiological and immunological studies point to remarkable heterogeneity in inflammation, lung pathology and pulmonary function among TB patients. Although environmental factors like smoking or exposure to silica among mineworkers [2–4, 7], differences in MTB virulence [143] or HIV co-infection [2, 8, 144] may contribute to this heterogeneity, variation in the host genes that regulate immune response to MTB could also be involved (figure 3). However, the literature is sparse in terms of the genetic correlates of lung damage in TB (table 3). Wang *et al.* [145] investigated a polymorphic site in the *MMP-1* promoter, which can consist of a single guanine nucleotide (1G) or have an insertion of a G (2G). Patients with the *MMP-1* 1G variant were more likely to have advanced lung fibrosis a year after TB treatment completion [145]. Other groups have demonstrated an association between *MMP-1* 1G and cavitary disease [146] and TB that is primarily endobronchial [147]. TB patients carrying the *MMP-1* 1G allele also had an increased risk for tracheobronchial stenosis following treatment [147]. The mechanism underlying lung damage in the *MMP-1* 1G carriers remains unclear, as it is the *MMP-1* 2G allele that introduces an Ets transcription binding site and increases *MMP-1* expression [167]. In line with the *MMP-1* 2G variant's functional role, a study found that patients with the *MMP-1* 2G/2G genotype had a 6.5-fold increased risk of permanent lesions following TB treatment *versus* patients with other genotypes at this locus [148]. However, this association was only in the presence of an additional variant in the monocyte chemoattractant protein (*MCP*)-1 promoter (*MCP-1* G/G). Patients harbouring both the *MCP-1* G/G and *MMP-1* 2G/2G genotypes had extensive fibrosis and increased prevalence of bronchiectasis at the end of TB treatment [148]. These studies, however, did not assess lung function to relate to genotype and lung pathology.

In contrast, studies have intensely interrogated genetic susceptibility for COPD [168]. Given the link between history of TB and COPD, we hypothesise that immunogenetic risk factors associated with COPD may be potential candidates for airflow obstruction after TB. For example, the *MMP-1* 2G variant discussed above in combination with a single nucleotide polymorphism (SNP) in *MMP-12* was associated with accelerated lung function decline in COPD patients [150]. Polymorphisms in *MMP-9* and *-12,* as well as *TIMP* genes have been linked to COPD and rapid FEV_1 decline [151–153, 169]. These variants may be relevant in the context of TB-associated lung impairment and should be examined further.

Variants in inflammatory cytokine genes have also been implicated in COPD. A meta-analysis of 36 studies demonstrated that the TNF-α -308A polymorphism increased risk of COPD in Asians [154]. In addition to being associated with greater yearly decline in FEV_1 and chronic bronchitis compared to those without the variant allele, the TNF-α -308A polymorphism was linked to elevated sputum levels of TNF-α, IL-8 and MPO in COPD patients [155]. Gene variants of pro-inflammatory markers such as *IL-8* [156], *TGF-β* [157] and *IL-6* [158] have been associated with airflow limitation in COPD. It is yet to be determined if all or any of these common genetic variants play a role in contributing to lung dysfunction in TB.

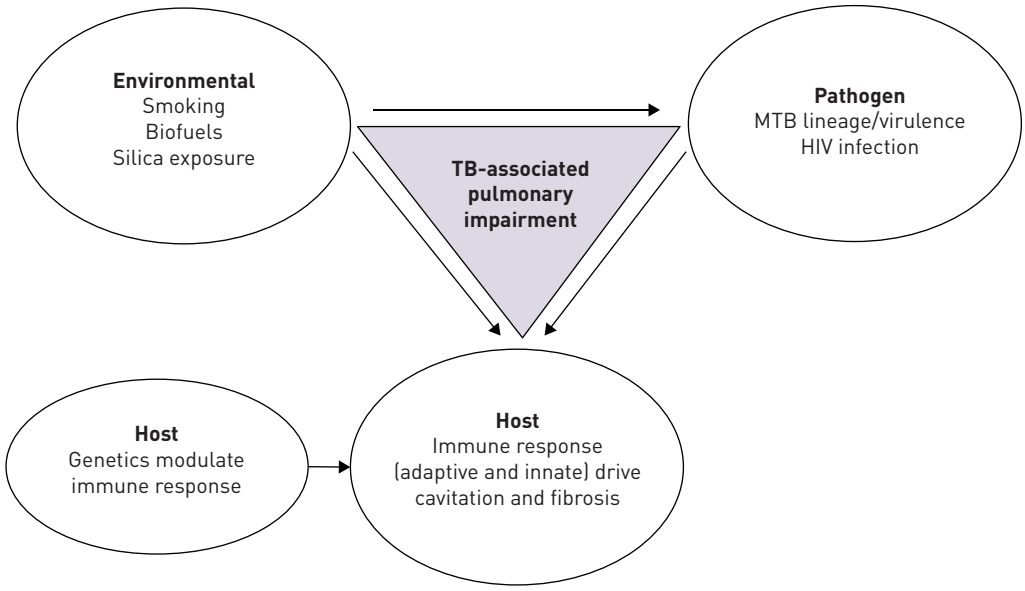

FIGURE 3 Conceptual model of factors that potentially contribute to lung impairment after tuberculosis (TB). MTB: *Mycobacterium tuberculosis*.

TABLE 3 Immunogenetic studies of lung dysfunction potentially relevant to pulmonary impairment after tuberculosis (TB)

Biomarker/gene	Polymorphism	Implication on lung pathology/function	Reference
TB			
MMP-1	MMP-1 -1607G (1G) (rs1799750)	Extensive fibrosis after 1 year of TB treatment Cavitary disease Endobronchial TB and tracheobronchial stenosis	[145–147]
MCP-1+MMP-1	MCP-1 -2518G (G/G) (rs1024611) MMP-1 -1607GG (2G/2G) Guanine insertion at this locus	Permanent lesions after TB treatment Fibrosis Bronchiectasis	[148]
TOLLIP	TOLLIP rs5743899 rs3750920	Decreased TOLLIP mRNA expression Increased inflammatory cytokine expression Increased risk for TB	[149]
COPD			
MMP-1+MMP-12	MMP-1 2G+MMP-12 nsSNP (rs652438)	Increased rate of lung function decline	[150]
MMP-9	MMP-9 -1562C/T	Increased risk of COPD in a Korean population	[151]
MMP-12	MMP-12 rs652438 and rs2276109	Severe (GOLD stage III) and very severe COPD (GOLD IV), lower FEV_1 %	[152]
TIMP-2	TIMP-2 +853G/A -418G/C	Increased risk for COPD Decreased transcription and stability of mRNA	[153]
TNF-α	TNF-α -308G/A (rs1800629)	Increased risk of COPD Increased yearly reduction in FEV_1 Chronic bronchitis Elevated TNF-α, IL-8, and myeloperoxidase in sputum	[154,155]
IL-8	IL-8 rs4073 rs2227306 rs2227307	Significant decrease in FEV_1 and FVC during follow-up of COPD patients	[156]
IPF			
TGF-β+TNF-α	TGFβ (rs1800469) +TNF-α (rs361525)	Additive effect on lung impairment measured as FEV_1	[157]
IL-6	IL-6 -174G/C	Decrease in FEV_1	[158]
IL-1RA	IL-1RN +2018C/T (rs419598) Variable number tandem repeat (VNTR)*2 rs2637988	Risk for fibrosing alveolitis and IPF Increased susceptibility for IPF Decreased IL-1RA mRNA levels that may predispose to IPF	[159, 160]
TNF-α	TNF-α -308G/A (rs1800629)	Fibrosing alveolitis risk	[159]
IL-6	IL-6 intron 4A/G	Lower carbon monoxide diffusion	[161]
TGF-β	TGF-β Codon 10T/C(rs1982073) Codon 25G/C(rs1800471)	Decreased gas exchange in IPF patients	[162, 163]
MUC5B	MUC5B rs35705950 rs868903	Associated with pulmonary fibrosis in genome-wide association studies Increased MUC5B expression	[164–166]
TOLLIP	TOLLIP rs5743890 rs111521887 rs5743894	Associated with reduced TOLLIP expression in lung tissue from IPF patients rs5743890 linked to mortality in IPF patients	

MMP: matrix metalloproteinase; MCP: monocyte chemoattractant protein; COPD: chronic obstructive pulmonary disease; TIMP: tissue inhibitor of metalloproteinase; TNF: tumour necrosis factor; IL: interleukin; IPF: idiopathic pulmonary fibrosis; TGF: transforming growth factor; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Immune mechanisms underlying fibrotic interstitial lung diseases, such as IPF, may overlap with those driving fibrogenesis in TB. Thus, it is plausible that common genetic variants implicated in IPF have a role in abnormal tissue repair, impaired gas exchange and restrictive ventilatory defects in TB patients. Notably, variants in the *IL-1* receptor antagonist and *TNF-α* genes have been associated with increased risk of IPF [159, 160]. A SNP in *IL-6* has been associated with decline in D_{LCO} in the lungs of IPF patients [161]. Furthermore, SNPs in the *TGF-β* gene were linked to decreased gas exchange in IPF [162, 163]. Moreover, multiple genome-wide association studies have implicated SNPs in *mucin 5B* (*MUC5B)*

and *TOLLIP*, which modulate innate immune responses, in IPF [164–166]. Genetic variation in *TOLLIP* is particularly interesting, given its role in negatively regulating the TGF-β [170] and Toll-like receptor signalling cascade [149]. TOLLIP deficiency leads to an increase in IL-6 and TNF-α secretion in mice and humans [149, 171]. Furthermore, individuals who harboured the *TOLLIP* rs5743899 or rs3750920 SNP had diminished *TOLLIP* mRNA expression, elevated levels of inflammatory cytokines and at an increased risk for TB [149]. However, these SNPs have not been examined in the context of lung pathology in TB or PIAT.

Future directions

It is evident from epidemiological studies that pulmonary impairment is relatively common among patients with a history of TB. Clinical trials investigating new drug regimens for TB should consider including lung function tests to evaluate the impact of these therapies on long-term pulmonary morbidity. Given the variety of lung function abnormalities, management of TB can potentially be pulmonary impairment specific and could target specific underlying immunopathological mechanisms. Furthermore, investigating the role of common variants in TB-associated lung injury may provide insight into the immunopathogenesis of PIAT. Genome-wide association studies combined with global transcriptomic analyses may also reveal novel biomarkers and networks of pathways associated with lung damage in TB.

Therapies that harness the host's immune response to supplement existing anti-TB treatment regimens have garnered interest [172]. Host-directed therapies that block inflammatory effectors and pathways involved in lung damage are a particularly attractive way to reverse lung injury and improve pulmonary function. However, the variability in inflammatory profiles and pulmonary outcomes between patients should be considered when evaluating host-directed therapies, as patients may not all benefit equally from a single treatment option. In fact, Tobin *et al.* [103] demonstrated that TB-meningitis patients carrying a *leukotriene A4 hydrolase* (*LTA4H)* gene variant associated with elevated TNF-α expression benefited the most from dexamethasone adjunctive therapy compared to those without this polymorphism. Personalised adjunctive host-directed therapies could improve TB treatment, where therapies against lung damage are tailored to target specific immune pathways based on the patient's inflammatory and immunogenetic profile. In addition, the potential relative benefit of host-directed therapies targeting elements of the inflammatory response early in the course of TB treatment *versus* anti-fibrotic therapies during TB resolution is currently unknown. These and other research priorities are detailed in table 4.

In conclusion, there is a critical need for translational studies to illuminate the immunopathogenesis of PIAT and inform prevention and therapeutic strategies. Genetic predisposition to pulmonary morbidity after TB should also be evaluated for a comprehensive understanding of this important outcome.

TABLE 4 Summary of key research priorities to address pulmonary impairment after tuberculosis (TB)

Epidemiological studies
Population-based studies that determine the prevalence of: 1) lung function defects by type (airflow obstruction, restrictive ventilatory defects, gas exchange abnormalities, *V'/Q* mismatch and mixed defects); and 2) lung damage by type (cavitation, fibrosis and bronchiectasis)
Investigate risk factors (host, environmental, pathogen) associated with PIAT
Measure impact of PIAT on quality of life
Determine the prevalence of PIAT and characterise lung deficits in specific patient populations, such as those co-infected with HIV, who have diabetes mellitus or are infected with multidrug-resistant TB
Basic/translational science
Delineate the immunopathogenesis of pulmonary cavitation, fibrosis and bronchiectasis in pulmonary TB
Determine the immunogenetic correlates of hyper-inflammation and tissue damage in pulmonary TB utilising genome-wide association studies similar to those in IPF and COPD
Identify key biomarkers or immune pathways as targets for immunomodulation to reduce lung pathology in pulmonary TB
Clinical/translational science
Diagnosis and diagnostic tests: investigate the utility of chest radiographs, CT, PET-CT, pulse oximetry, 6-min walk test and PFTs prior and post-TB treatment in diagnosing those at increased risk for PIAT
Prevention and treatment:
Develop effective vaccines to prevent TB and lung tissue damage post infection
Develop novel drugs and biologics for TB that not only shorten treatment duration, but also reduce lung tissue injury
Investigate the use of adjunctive host-directed therapy to treat TB and associated lung pathology
Evaluate the efficacy of the use of common COPD and anti-fibrotic medications in preventing and/or treatment of post-TB lung injury
These initiatives would be informed by studies that address the basic/translational science priorities described above

V'/Q: ventilation/perfusion; PIAT: pulmonary impairment after TB; IPF: idiopathic pulmonary fibrosis; COPD: chronic obstructive pulmonary disease; CT: computed tomography; PET: positron emission tomography; PFT: pulmonary function test.

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