Review Article

Advances in molecular mechanisms of interaction between *Mycobacterium tuberculosis* and lung cancer: a narrative review

Kunlong Xiong[1,2#^], Wenwen Sun[1,2#], Yayi He[2,3], Lin Fan[1,2^]

[1]Shanghai Clinical Research Center for Infectious Disease (Tuberculosis), Department of Tuberculosis, Shanghai Key Laboratory of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; [2]Department of Tuberculosis, Tongji University, Shanghai, China; [3]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: Y He; (II) Administrative support: Y He, L Fan; (III) Provision of study materials or patients: K Xiong, W Sun; (IV) Collection and assembly of data: K Xiong; (V) Data analysis and interpretation: K Xiong, W Sun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yayi He. Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, No. 507 Zhengmin Road, Shanghai 200433, China. Email: yayi.he@tongji.edu.cn; Lin Fan. Shanghai Clinical Research Center for Infectious Disease (Tuberculosis), Department of Tuberculosis, Shanghai Key Laboratory of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China. Email: fanlinsj@163.com.

Objective: We systematically review the molecular mechanism of the interaction between lung cancer (LC) and tuberculosis (TB), and put forward the existing problems in order to provide suggestions for early intervention and future research direction.

Background: TB and LC are two global public health problems affecting human health. LC is the main cause of cancer-related death worldwide and TB is one of the leading causes of death among infectious diseases, especially in resource-poor areas. Previous studies have suggested that a history of TB may be associated with an increased risk of LC. With the improvement of LC treatment, the occurrence of pulmonary tuberculosis in the course of LC treatment is also frequently reported recently.

Methods: The molecular immunological mechanisms of interaction between LC and TB, and related epidemiological literature are reviewed. The research progress and problems to be solved are summarized.

Conclusions: Chronic inflammation, immune abnormalities, scar formation, gene mutations and drug effects caused by TB may be associated with the occurrence of LC induced by abnormalities in various molecular pathways. LC and decreased immunity during treatment may also increase the risk of latent TB activation or new TB infection through immune pathways. Data on dual burden areas of TB and LC are still lacking, and more clinical studies are needed to elucidate the association.

Keywords: Tuberculosis (TB); lung cancer; inflammation; epidermal growth factor receptor (EGFR); PD-1; microflora

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^ ORCID: Kunlong Xiong, 0000-0002-3312-227X; Lin Fan, 0000-0002-9411-496X.

Introduction

Tuberculosis (TB), caused by the bacillus *Mycobacterium tuberculosis* (MTB), is one of the main sources of morbidity and mortality from infectious disease (ranking even higher than HIV), infecting nearly a quarter of the whole population worldwide, and causes more than 1.4 million deaths in 2019, according to the Global Tuberculosis Report 2020 from World Health Organization (WHO) (1). MTB mainly infected the lung, known as pulmonary tuberculosis (PTB). Most people infected with MTB remain asymptomatic and without any observed lesions, known as latent tuberculosis infection (LTBI), with a lifetime risk of developing active TB of about 5–10% (1).

Lung cancer (LC) also remains the leading cause of tumor-related death globally. There were about 2.2 million new cases and 1.8 million deaths caused by LC in 2020 (2). LC is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 80–85% of LC, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (3-5). In the last two decades, the 5-year survival rate of NSCLC has been lower than 20%, while the 5-year survival rate of SCLC is close to 5% (5-7).

As an important factor in causing tumors, carcinogenic infections are responsible for about 15.4% (2.2 million) of 14 million new cases of cancer in 2012 (8,9). And with the improvement of the treatment of LC, the wide application of immunotherapy and the prolonged survival of LC patients, the co-existence of TB and LC is becoming more common in clinical practice, especially in developing countries with high burden of TB. Previous study had divided the coexistence of TB and LC into three types: (I) no relationship between PTB and LC; (II) LC developed on the basis of tuberculous lesions, induced by bronchial/alveolar malformations and epithelial dysplasia; (III) reactivation of TB during LC progression and treatment (10).

Cough, expectoration, hemoptysis, chest pain, shortness of breath, fever, and abnormal radiological findings are common symptoms of both LC and TB, leading to a challenge in the diagnosis of the diseases. Systemic chemotherapy and immunotherapy commonly accepted in LC are highly correlated with the development of TB (11). Previous studies have shown that a history of PTB is associated with an increased risk of LC (12-19), or the survival and mortality of LC (20,21). TB, as a risk factor for LC has been widely studied and its pathogenesis is complex, mainly focusing on chronic inflammatory stimulation, immune dysfunction, scar calcification, gene mutation, etc., but the specific mechanism has not been fully elucidated. In the present study, the molecular mechanism and possible interaction between LC and TB were reviewed, the existing problems were proposed, in order to provide the basis for early identification and intervention of patients with LC complicated PTB, especially in areas with high TB burdens.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-465).

Epidemiology correlations between TB and LC

There were about 10 million TB patients in 2019 globally, especially in India and China, the highest and the second-highest TB burden countries, with an estimated 2.6 or 0.8 million TB incidence, respectively (1). A large amounts of epidemiological data have showed that PTB could be closely related to LC (shown in *Table 1*). Cicėnas *et al.* (10) found that PTB co-exists with LC, which is a rare clinical observation compared to the single incidence of PTB or LC, about 2.1% operated LC patients were diagnosed with complicated PTB. Everatt *et al.* (12) studied the risk of LC in a cohort of 21,986 PTB patients in Lithuania. The results showed that during follow-up, 477 TB patients developed LC, and patients with a history of TB had a 3.5-fold increased risk of LC. There were also some other retrospective cohort or prospective longitudinal studies showed the pre-existing PTB associated with an increased risk of LC (13-17).

Several meta-analyses were also performed to estimate the association between TB and LC. Liang and collogues (18) performed a systematic review and meta-analysis of 37 case-control and 4 cohort studies to assess the association between LC risk and pre-existing TB. The results showed pre-existing TB had a significant association with the increased LC risk [relative risk (RR): 1.7; 95% confidence interval (CI): 1.5–2.0]. Moreover, the elevated LC risk persisted 2-fold higher after over two decades since TB was diagnosed. Brenner *et al.* (19) conducted a meta-analysis to survey the epidemiologic clues about the correlation between pre-existing TB and the increased risk of LC, after analyzing for 30 studies, a significantly increased LC risk was found in patients with pre-existing TB compared to the subjects without pre-existing TB (RR: 1.8; 95% CI: 1.5–2.1). A meta-analysis performed by Leung *et al.* (9) including 52,480 cancer cases showed that TB was associated with LC (RR: 1.7; 95%

Table 1 Published studies about epidemiology correlations between tuberculosis and lung cancer

Investigator (year)	Cohort size/number of controls	Methods	Results	Conclusions	Ref.
Leung (2020)	52,480 cancer cases	Meta-analysis	LC RR was 1.7 (95% CI: 1.5–2.0) in TB patients.	TB was associated with lung cancer.	(9)
Everatt (2016)	21,986 TB patients	Retrospective study	477 TB patients developed LC, and 3.5-fold increase risk of LC in subjects with a history of TB.	The excess risk of LC in the TB cohort is associated with multiple factors.	(12)
Oh (2020)	2,640 patients with pre-existing TB, 17,612 controls	Retrospective cohort study	LC HR was 3.2 (95% CI: 1.9–5.6) in PTB patients.	A higher risk of LC was found in pre-existing TB patients.	(13)
Wu (2011)	5,657 patients with pre-existing TB, 23,984 controls	Retrospective cohort study	LC IRR was 1.8 (95% CI: 1.3–2.3) in PTB patients.	PTB is associated with an increased risk of LC.	(14)
Yu (2011)	4,480 TB patients, 712,392 controls	Prospective longitudinal study	TB patients had a nearly 11-fold higher incidence than controls (26.3 *vs.* 2.4 per 10,000 person-years).	TB patients had an increased LC risk.	(15)
Zheng (1987)	1,405 LC patients, 1,495 controls	Prospective longitudinal study	LC OR was 1.5 in TB cohort and remained 2.5-fold higher after the TB diagnosis within the past 20 years.	TB may predispose to LC.	(16)
Shiels (2011)	273 male smokers with TB, 28,860 male smokers with non-TB	Prospective longitudinal study	LC HR was 2 in TB patients (95% CI: 1.5–2.7), and LC risk was highest at about 2 years after TB diagnosis (HR: 5.0; 95% CI: 3.0–8.5), but the risk remained raised at the longer latencies (HR: 1.5; 95% CI: 1.1–2.2).	TB is associated with increased LC risk in male smokers.	(17)
Liang (2009)	19,143 TB cases, 118,191 controls	Meta-analysis	LC RR was 1.7 (95% CI: 1.5–2.0) in TB patients, and passive smoking or exposure of the environmental smoke did not confound the association [RR was 1.8 (95% CI:1.4–2.2) and 2.9 (95% CI: 1.6–5.3), respectively].	TB had a direct relation with LC, especially adenocarcinomas.	(18)
Brenner (2011)	30 studies, 82,716 cases	Meta-analysis	LC RR was 1.8 (95% CI: 1.5–2.1) in pre-existing TB patients.	PTB is associated with an increased risk of LC.	(19)
Littman (2004)	17,698 smokers	Prospective longitudinal study	Pre-existing of pulmonary emphysema or chronic bronchitis, rather than TB, was more likely to be associated with LC in smoking subjects.	Pre-existing TB had no correlation with LC.	(22)
Engels (2009)	246 TB patients, 42,176 no-TB cases	Retrospective cohort study	LC HR was 9.7 (95% CI: 4.8–19) in TB patients within 5 years after TB diagnosis, the mortality of LC was higher in TB patients than in LC patients without a history of TB (25 *vs.* 3.1 per 1,000 person-years).	TB was an important risk factor for LC, and LC mortality was higher in TB patients.	(20)

Table 1 (*continued*)

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Investigator (year)	Cohort size/number of controls	Methods	Results	Conclusions	Ref.
Heuvers (2012)	214 LC patients, 7,769 subjects without LC	Retrospective cohort study	13 of the 214 LC patients was reported to have a history of TB, and the survival of the LC patients with pre-existing TB was significantly shorter (HR: 2.4, 95% CI: 1.1–4.9) than those without with a difference in means of 311 days.	Pre-existing TB may be an important prognostic factor for the survival of LC.	(21)
Su (2016)	11,522 LTBI subjects, 46,088 matched subjects	Retrospective cohort study	LC HR was 2.7 in TB contacts.	LTBI cohorts had an increased lung cancer incidence.	(23)

TB, tuberculosis; LC, lung cancer; HR, hazard ratio; CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk; LTBI, latent tuberculosis infection.

CI: 1.5–2.0). What's more, LTBI cohort was also reported with an increased incidence of LC compared to comparison cohort [hazard ratio (HR): 2.7] (23).

Although most of related studies showed an increased LC risk among individuals with PTB, a study (22) in North America involved 17,698 smokers reported that the pre-existing of pulmonary emphysema or chronic bronchitis, rather than other lung diseases (such as TB, asbestosis, asthma), was more likely to be associated with LC in smoking subjects (adjusted HR: 1.3; 95% CI: 1.1–1.5).

In addition, whether TB was associated with subsequent LC survival and mortality was also analyzed by some studies. A retrospective cohort study (20) in China recruited 42,422 farmers to evaluate the relationship between PTB and the mortality of subsequent LC. The results showed that the mortality of LC was higher in patients with PTB history (25 per 1,000 person-years) than in LC patients without a history of PTB (3.1 per 1,000 person-years), which was especially obvious within the first 5-year after the diagnosis of PTB (HR ranging from 6.7 to13) and remained robust within the 5–9.9 years (HR: 3.4; 95% CI: 1.3–9.1), or more than 10 years (HR:3.0; 95% CI: 1.3–7.3). Based on the data from "The Rotterdam Study" (24), a population-based retrospective cohort study, with 214 LC patients and 7,769 subjects without LC included, Heuvers *et al.* (21) attempted to examine whether pre-existing PTB was an independent risk factor for LC survival. The results showed that 13 of the 214 LC patients was reported to have a history of PTB, and the survival of the LC patients with pre-existing PTB was significantly shorter (HR: 2.4, 95% CI: 1.1–4.9) than those without with a difference in means of 311 days (*Table 1*).

Mechanisms of chronic inflammation elicited by MTB infection in tumorigenesis

Long-term pathogen-induced chronic inflammatory stimulation will increase the risk of cancer. Helicobacter pylori, hepatitis virus, human papillomavirus and Epstein-Barr virus are common susceptible carcinogens (9). The continuous inflammatory stimulation and tissue damage/repair caused by MTB infection are also important reasons for the development of LC. After infection, alveolar macrophages endocytose invasive MTB and sequestrate them in the phagosome (25). However, MTB has evolved special mechanisms to escape the phagosome and persist in cytoplasm of macrophages, leading to the formation of granulomas (26). Since the ability of immune cells (e.g., macrophages, T cells, B cells), which is recruited by MTB-infected macrophages within or around the granulomas, to kill mycobacterium can resist the aggressive invasiveness of MTB, the growth of mycobacteria is slowed down and the non-replicating bacteria in the macrophage remain dormant, leading to persistent chronic inflammation with more vascularized tissues surrounding, recruited macrophages, and T cells (27-29). Respiratory inflammation may persist for several months before PTB diagnosis and during the anti-TB treatment. Inflammatory lung diseases or lung infections (such as PTB, bacterial pneumonia) have been reported to be the elevated risks of LC (12-19,30). After invading, MTB induces the production of tumor necrosis factor (TNF), interferon-gamma (IFN-γ), interleukins in host. TNF and IL-6 promote antiapoptotic genes expression through the nuclear factor kappa B (NF-κB) pathway in pulmonary epithelial cells, contributing to the development of

cancer (30-32).

Tumor microenvironment (TME), which is orchestrated primarily by infiltrating inflammatory cells, plays a role in promoting cell proliferation, survival and migration, leading to the tumorigenesis (33). TME and TB granulomas share the same central theme, hijacked macrophage polarization programs and exhausted phenotypes of T cells (28). There are numerous immune checkpoints enriched in exhausted T cells, such as PD-1, LAG-3, TIM-3, and CTLA-4 (34), which play a central role in T cell response inhibition. Relieving the immunosuppressive factors in the TME is beneficial to restore the functional inhibition of exhausted T cells and tumor therapy. Studies have reported that PD-1/PD-L1 targeted blocking antibodies are entering first-line therapy in recent years, for the vibrant survival benefits they have offered to NSCLC patients (35,36). Thus, the exhausted T cell phenotype induced by MTB contributes to the development of tumors.

Cancer formation develops from "initiation" and "promotion", and these two subthreshold tumor states are usually caused by chemical or viral carcinogens, leading to somatic cell changes (37). The "initiation" state involves irreversible changes in DNA that can persist in normal cells until the second state "promotes" occurs. The "promoter" state can arise from chemical irritants exposure of initiated cells, such as the release of phobol esters due to chronic inflammation. The "promoter" state promotes cell proliferation, recruitment of inflammatory cells, production of reactive oxygen species (ROS), oxidative damage of DNA, and reduction of DNA repair (33). Chronic inflammation induced by MTB promotes cell death, cell proliferation, excessive ROS production, DNA damage and DNA repair, which persist in chronic inflammatory tissues, resulting in loss of normal growth control of DNA replication and proliferation of cells. The level of ROS is increased in different types of tumor cells, and the increased ROS is believed to cause DNA damage, generate mutagenic mediators (such as peroxynitrite), promote genetic instability, and thus carcinogenesis (38-40).

Substantial and prolonged pulmonary inflammation induced by TB leads to repeated tissue damage and repair, forming fibrotic scarring, which is associated with the increased LC risk (17,41,42). Tuberculous fibrosis may enhance the tumorigenic potential of lung cells through the NOX4-autophagy axis was documented in mouse model recently (43). Inflammatory monocytes (IMs) (referred as to phenotype "$CCR2^{high}CD14^{+}CD16^{low}$" in humans) are found in LC and play a crucial role in tumor-promoting and scar tissue formation (44-46). Lung squamous cell carcinomas (SCC) is a major subtype of LC, characterized by low survival rate and dense recruitment of the IMs, which is adequate for the distant metastasis of SCC (46). Tumors recruit IMs through secretion of monocyte chemotactic protein-1 (CCL-2) (46). Increased CCL-2 is also found in PTB patients (47). IMs can differentiate into dendritic cells (DCs) or tumor-associated macrophages (TAMs), which can be classified as M2-like macrophages and play an important role in tumor-promoting (45,48-52). For example, vascular endothelial growth factor A (VEGF-A), IL-6 and epidermal growth factor (EGF), Factor XIIIA produced by IM-derived TAMs play important roles in promoting the stemness and migration feature of tumor cells, paracrine responses in the TME, and SCC cells invasion and metastases trough the scaffold offered by the cross-linking of fibrin, respectively. In conclusion, chronic inflammation induced by MTB may be involved in the development of LC through exhausted T cell phenotype, DNA damage and repair, ROS production, tuberculous granuloma, tuberculous fibrosis, and IMs infiltration (*Figure 1*).

M2 polarization of macrophages induced by MTB may lead to LC

TAMs are the main component of infiltrated immune cells in TME. Macrophages are generally categorized to M1 (drive inflammation) or M2 (anti-inflammatory and promoting to wound healing) types, and TAMs are typically polarized into M2-like phenotype (52-57). The M1-like macrophages are induced by Th1 cytokines [including colony stimulating factor 2 (CSF-2), TNF-α, IFN-γ] or bacterial lipopolysaccharide, a toll-like receptor ligand (58,59). M1-like macrophages respond to infected pathogens and cancer cells by secreting ROS and some cytokines (such as TNF-α, IL-6, IL-23, and IL-12) to response against infected pathogens and cancer cells (60,61). Thus, an increased number of M1-like macrophages is usually associated with a favorable prognosis of cancer disease. M2-like macrophages, whose polarization is induced by Th2-derived cytokines (including IL-4, IL-13) or immunosuppressants (such as IL-10, TGF-β, glucocorticoids), are known to suppress inflammatory reaction and promote tissue regeneration through immunotolerance, immune modulation, dead cell debris scavenging and tissue remodeling (62,63).

In cancer, M2-like macrophages contribute to increased expression of angiogenesis and immunosuppressive molecules (including IL-10, PD-L1, and TGF-β) that

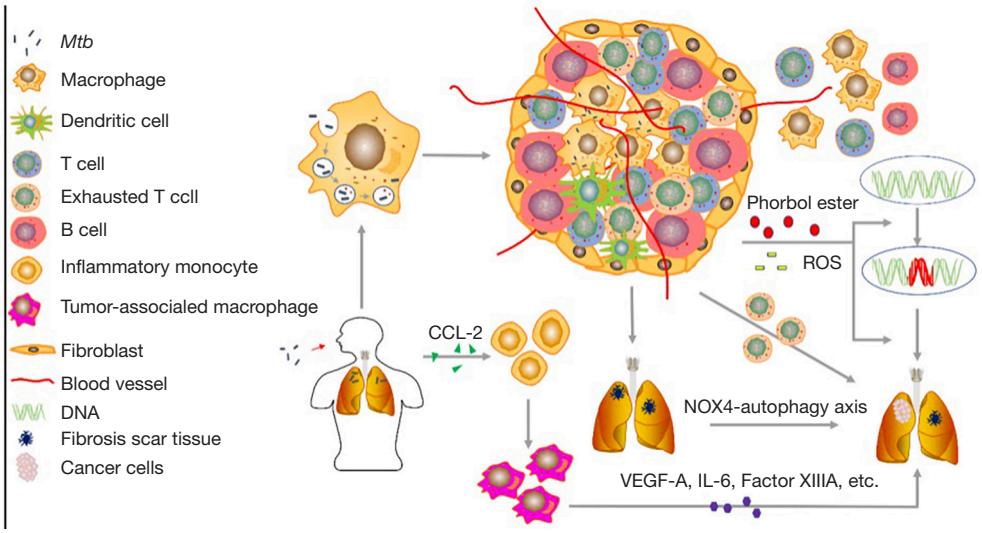

Figure 1 Chronic inflammation elicited by *Mycobacterium tuberculosis* (MTB) may be involved in the development of lung cancer (LC) through exhausted T cell phenotype, DNA damage and repair, reactive oxygen species (ROS) production, tuberculosis (TB) granuloma, tuberculous fibrosis formation and IMs infiltration. In the early stage of infection, the endocytosed infected MTB escape the phagosome of alveolar macrophages leads to the formation of granuloma, which vascularizes surrounding tissues and recruits immune cells, contributes to the prolonged inflammation. The exhausted T cells enriched in granuloma and the chronic inflammation induced ROS and chemical irritants releasing promote the occurrence of LC. There are a large number of immune checkpoints expression in exhausted T cells, which play a central role in inhibiting the T cell response and facilitating tumor progression. LC can also develop from fibrotic scar induced by MTB-induced lengthy pulmonary inflammation through mechanisms like NOX4-autophagy axis enhances the tumorigenic potential of lung cells. The TB patients have an increased expression level of monocyte chemoattractant protein-1 (CCL-2), which can recruit inflammatory monocytes (IMs). IMs can differentiate into tumor-associated macrophages (TAMs), and IMs-derived TAMs contribute to tumorigenesis through vascular endothelial growth factor A (VEGF-A), IL-6 and epidermal growth factor (EGF) or Factor XIIIA.

promote tumor cell growth (58). A high degree of M2-like TAMs infiltration is closely associated with tumor progression, invasion, metastasis, and resistance to cancer therapy (64-66). Xu *et al.* (67) found that TAMs, with M2-like phenotype that had a significant effect on external therapy resistance of anti-Her2/neu antibody therapy, can be skewed to M1-like polarized phenotype when anti-Her2/neu antibody therapy combined with targeted delivery of IL-21, and then overcomes anti-Her2/Neu resistance.

The polarization state of macrophage is not fixed, other cells or pathogens can alter the polarization state through multiple signals produced by them (68). In the early phase of PTB, the M1 phenotype of macrophages is upregulated, while the M2 phenotype is dominant in the intermediate and late stages (63). M1-like polarization of macrophages is included with enhanced phagocytosis, increased secretion levels of pro-inflammatory cytokines, and elevated production of nitric oxide (NO) in non-specific host immune response to infected intracellular bacteria (63,69). The susceptibility and progression of PTB was reported to be associated with elevated levels of type-2 inflammatory response signals such as IL-4, IL-13 or IL-10 (56). Successful treatment of PTB shifts the inflammatory atmosphere in infected patients from type-2 back to type-1 (70,71). In addition, it has been reported that NO can strongly inhibit the proliferation of human A431 tumor cells (72). Therefore, M1 phenotype polarization of macrophages is deleterious for both tumor cells and MTB. To counteract the "detrimental" effects of M1-like macrophages, MTB blocks M1 polarization through the bystander effect mediated transcription inhibition of IFN-γ that IL-6 participates in Ref. (73), leading to the elevated level of M2-like macrophages in TB. M2-like polarization of macrophages, which is characterized by low IL-12 expression and high IL-10 expression, drives the TME skewing to an anti-inflammatory state (28,53). M2 macrophages can help recruit Tregs (regulatory T-cells) into TME through CCR4 (C-C chemokine receptor 4) (74). M2 TAMs are reported to

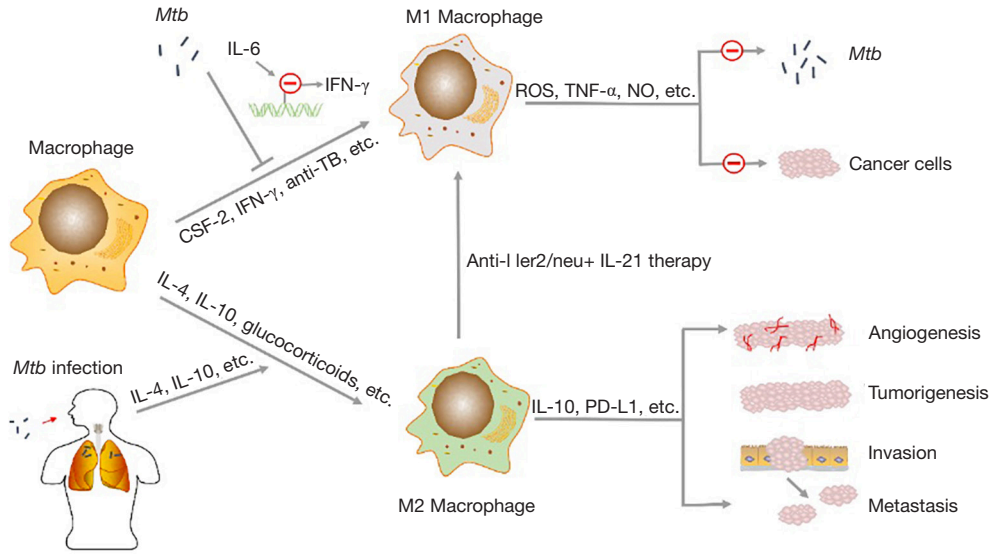

Figure 2 M2 polarization of macrophages induced by *Mycobacterium tuberculosis* (MTB) in lung cancer (LC): macrophages are generally categorized to M1 or M2 phenotype. M1-like macrophages, induced by Th1 cytokines such as colony stimulating factor (CSF)-2, TNF-α, and IFN-γ, are associate with pro-inflammatory and response against infected pathogens and cancer cells through ROS, TNF-α, IL-6, NO, etc. M2-like macrophages, induced by Th2 cytokines such as IL-4 and IL-13, contribute to angiogenesis and increased expression of immunosuppressive molecules to promote tumor cell growth, invasion, metastases. The M2 phenotype dominates in the intermediate and late phases of tuberculosis (TB), and raised levels of type-2 inflammatory response signals such as IL-4, IL-13 or IL-10 raised in TB patients, leading to the occurrence and progression of LC. MTB develops a relevant strategy to block M1 polarization through IL-6 involved bystander effect-mediated inhibition of the transcription of IFN-γ. While combining anti-Her2/neu antibody with targeted delivery of can skew M2-like macrophages to M1 phenotypes, and anti-TB therapy can shift the inflammatory atmosphere type-2 back to type-1, thus increase M1-like macrophages in PTB patients.

express more PD-L1 and CTLA4, the immune checkpoints for CTLs (cytotoxic T-cells), weakening the ability of CTLs to eliminate cancer cells (68,75). In addition, M2 TAMs express TGF-β, EGF, the molecules play roles in inhibiting apoptosis and prompting tumor cells proliferation to affect tumor progress directly (68). In conclusion, the M2-like phenotype polarization of macrophages, which is dominated in the intermediate and late phases of TB, may be one of the causes of pulmonary neoplasia (*Figure 2*).

TB may be associated with LC through epidermal growth factor receptor (EGFR) gene mutations and epiregulin production

EGFR, a transmembrane glycoprotein that belongs to the HER family (human EGFR related family), participates in numerous biological processes, cell proliferation and survival included, and the mutations of EGFR gene are the first identified driver mutation in LC (76,77). EGFR usually forms dimers with other members of HER family (including HER1/EGFR/erbB1, HER2/erbB2, HER/erbB3, and HER4/erbB4) or other EGFRs (78,79). After binding to its ligand, EGFR is auto-phosphorylated at its tyrosine residues, followed by the activation of some downstream signaling pathways, and get involved in various cellular processes such as cell proliferation, apoptosis and survival (78). Gene amplifications or mutations can generate continuously activated EGFR, leading to tumorigenesis (80,81). The prevalence of EGFR mutations in lung adenocarcinoma patients ranges from 10% to 78%, depending on ethnicity and geographic location, such as 30% to 40% in Asian patients and 15% in white patients (82,83). The vast majority (for more than 90%) of activating EGFR mutations are known as either the deletion mutations of Exon 19 or the point mutations of Exon 21 (L858R), and patients with these two mutations are both highly sensitive to EGFR tyrosine kinase inhibitors (TKIs) (84,85).

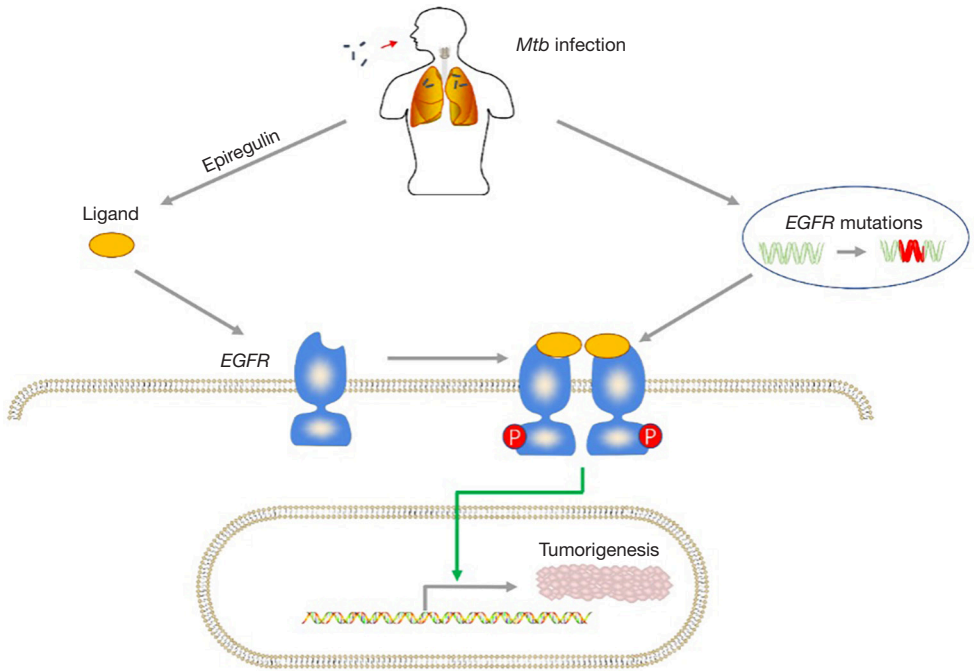

Figure 3 Epidermal growth factor receptor (EGFR) mutations induced by tuberculosis (TB) in lung cancer (LC): EGFR autophosphorylates at their tyrosine residues after binding to their ligands. The activated EGFR activates many downstream signaling pathways, such as cell proliferation, apoptosis, and survival. EGFR mutations can generate continuously activated EGFR, which leads to tumorigenesis. Patients with pre-existing tuberculosis (TB) have an increased frequency of EGFR mutations, and *Mycobacterium tuberculosis* (MTB)-infected macrophages play a role in the production of epiregulin, a most potent ligand for EGFR, thus promote the occurrence of LC.

A study (86) from South Korea showed that in patients with lung adenocarcinoma, pre-existing TB lesions are significantly associated with increased EGFR mutation rates, particularly exon 19 deletion. The mutation rate in patients with the main mass of the same lobe or different lobes of the ipsilateral lung was significantly higher than that in patients with the main mass of the contralateral lung. In addition, patients treated with EGFR-TKIs for TB-associated adenocarcinoma have poorer treatment response and survival compared with non-TB-associated patients (86). Luo *et al.* (87) evaluated the correlation of EGFR mutation outcomes available in 275 patients in Taiwan. In their study, a total of 191 patients (69.5%) had EGFR mutations, and the mutation rate was significantly higher in patients with old PTB lesions than that in non-PTB patients (80.6% *vs.* 65.5%, P=0.018). In addition, they reported a higher rate of exon 19 deletion in patients with older PTB lesions than that in patients without PTB (68% *vs.* 34%, P<0.001). Chang *et al.* (88) reviewed 8,265 patients and found that a history of PTB was associated with a poor clinical response to EGFR-TKIs in men and a better response in women. The reason why patients with PTB-associated adenocarcinoma have poor response to EGFR-TKIs remains unclear. However, aggressive phenotypes caused by chronic inflammation may be a possible explanation. Nalbandian *et al.* (41) found that MTB-infected macrophages induce DNA damage nearby and produce a most potent ligand for EGFR, epiregulin, to induce carcinogenesis. Thus, PTB-induced EGFR mutations and epiregulin production maybe also be involved in lung carcinogenesis. Taken together, TB-induced EGFR mutations and epiregulin production maybe also contribute to the carcinogenesis in lung (*Figure 3*).

The occurrence of PTB during anti-PD-1/PD-L1 therapy

Immune checkpoint inhibitors (ICIs) are a class of immunotherapy drugs that have made great breakthroughs in the field of tumor therapy in recent years, which is a therapeutic method to kill tumor cells by regulating T cell activity through a series of pathways such as co-inhibition

or co-stimulation of signals. Checkpoint inhibitors target cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), PD-1, and PD-L1 were currently approved. Interestingly, the roles of ICIs in infectious diseases have also been studied (89). PTB reactivation is recognized as an adverse reaction that is attributable to anticancer biologics and TNF-α inhibitors (90). PTB recurrences are more common in patients with hematologic malignancies than those with solid tumors. In solid tumors, the reactivation rate of PTB is highest in LC, followed by gastric cancer, breast cancer, liver cancer and colon cancer (90). There are increasing reports of MTB activation during ICIs immunotherapy (91). A study summarized 15 related cases from 12 retrieved articles showed that all the patients were either Caucasians or Asian and aged 49 to 87 years, with a male preponderance, and 5 cases of them were diagnosed as metastatic NSCLC (92).

Most patients infected with MTB may remain a latent state, and only about 10% of them may develop an active PTB (1). The containment of the infection is mediated by the interaction between cytokines and macrophages and T lymphocytes (CD4 and CD8) (93). Immune dysfunction (organ transplant patients and patients receiving immunosuppressive therapy) is the most critical risk factor for MTB activation (94). In a mouse model, PD-1-deficient individuals exposed to MTB aerosol were significantly sensitive to MTB infection and high bacterial load accompanied by significantly increased proinflammatory cytokines like IL-1, IL-6, IL-17 (95). Compared with the control group, the survival rate of PD-1-deficient mice was also significantly reduced. These reveal that excessive inflammatory response due to PD-1 dysfunction is detrimental for host to control MTB, while another study shown that the activating immune system through blocking PD-1/PD-L1 can effectively target inhibit certain viral, bacterial, and fungal pathogens by limiting T cell dysfunction (89). A case report (96) showed that nivolumab (an anti-PD-1antibody immune checkpoint inhibitor) therapy may promote the progression of *Mycobacterium abscess* disease. In addition, Fujita *et al.* (97) reported a patient with SCLC developed bacteriologically confirmed PTB after eight cycles of nivolumab administration. Thus, improper interventions of PD-1/PD-L1 function may be detrimental for MTB control, even resulting in PTB reactivation.

There is currently no clear evidence of the need for LTBI screening tests and preventive antituberculosis therapy before immunotherapy. We believe that relevant research is necessary in the future, especially in countries with high TB burdens (92).

Microbial dysbiosis caused by the long-time anti-TB chemotherapy may lead to LC

Microflora is known to participate in maintaining the homeostasis and the regulation of immune responses in hosts. Although it has been long considered that the healthy lung tissues were sterile, a number of microbial species were found in healthy lung tissues through high-throughput sequencing, the next generation sequencing (NGS) technologies (98,99). The microflora in lung plays essential roles in physiological process in hosts, such as exercising effects on mucosal immunity, promoting the recruitment of neutrophil to induce immune tolerance, affecting the secretion of TLR2-dependent pro-inflammatory cytokines, and the release of an antimicrobial peptide human β-defensin-2 (hBD2) (100). Brown *et al.* (101) showed that microbiota enhances respiratory defenses through GM-CSF, whose generation in lung is primed by microbiota through IL-17A in response to infection. GM-CSF signaling can enhance the ability of alveolar macrophages to kill invasive pathogens (101). Due to the invasion of the tumor and the use of cytotoxic drugs, microbial dysbiosis may occurred in LC patients. A study (102) found that MTB related functional pathways were enriched in LC patients through 16S rRNA gene analysis of saliva microbiota. Correspondingly, the long-term anti-TB chemotherapy required makes the long-term detrimental effects on the microbiota (103). It has been widely acknowledged that the interaction between host immunity and external environmental factors, among which microbes is deeply involved in maintaining microecological balance and regulating the immune responses in host to multiple treatment interference, contributes to LC (104,105). Therefore, LC may cause the reactivation of LTBI and increase the susceptibility of PTB by weakening local immunity. The microbial dysbiosis caused by the long-time anti-TB chemotherapy may also lead to the occurrence of LC.

TB may be immunologically related to LC through Bacille Calmette-Guerin (BCG)

BCG is a live vaccine made from a suspension of attenuated *Mycobacterium bovis* bacilli and is the only approved vaccine for the prevention of MTB. BCG can activate an innate immune system, macrophages particularly, which is beneficial to be a preventive and therapeutic vaccine in TB and cancer.

Trained innate immunity (TI) is acknowledged to be NOD2 receptor dependent. As a cytoplasmic pathogen recognition receptor (PRR), NOD2 receptor recognizes muramyl dipeptide (MDP) from bacterial peptidoglycan (106). MDP triggers NOD2 receptors to increase the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, resulting in non-specific protection against MTB infection and other non-mycobacterial infections (107-110). Innate immune training occurs in both monocytes and other cells (e.g., NK cells) (111). However, BCG-induced trained innate immunity can still occur in the absence of a NOD receptor, which is thought to help recruit activated macrophages into lung to make the innate immune system hyperactivated after subcutaneous vaccination (107). Intravesical BCG has been seen as one of the most effective therapies for non-muscular invasive bladder cancer (NMIBC), the most common type (75%) of bladder cancer, since firstly reported by Morales *et al.* in 1976 (112,113). A recent study (114) enrolled 1,540 BCG vaccinated participants and 1,423 placebo recipients showed a similar overall incidence of cancers, including lymphoma and leukemia, among BCG vaccinators and placebo recipients (HR: 0.8; 95% CI: 0.7–1.0). However, after adjusting for factors such as gender, region, alcohol use, smoking and history of PTB, the incidence of LC in the BCG vaccinated group (18.2 per 100,000 person-years) was significantly lower than that in the placebo group (45.4 per 100,000 person-years) (HR: 0.4; 95% CI: 0.2–0.7; P=0.005). BCG is the only MTB protective vaccine and the gold standard adjuvant in the treatment of NMIBC, suggesting that there are some undefined immunosuppressive mechanisms between PTB and LC, which may be one of the future research directions.

Conclusions

Epidemiological studies have confirmed the relationship between TB and LC. Chronic inflammatory stimulation, immune abnormality, scar formation, gene mutation and drug influence caused by MTB may be related to the occurrence of LC. LC and reduced immunity during treatment may also increase the risk of LTBI activation or new MTB infections. However, the underlying mechanisms by which the two diseases interact have not been fully elucidated. The rapid development of immunotherapy has brought the promise of treatment for patients with advanced LC, but the subsequent recurrence of PTB has attracted the attention of researchers. Existing researches are mainly focused on developed countries and data from areas with the double burden of PTB and LC are still lacking, therefore, more clinical studies in different epidemiological Settings are needed to elucidate the underlying mechanisms of influence between these two diseases.

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