Peer Review File

Reviewer A

Xiong and Sun reviewed the potential molecular mechanisms behind the association between tuberculosis and lung cancer. The topic is of importance. The manuscript is well-written and easy to follow. I only have minor comments for the manuscript:

In the introduction section, the authors provided background information on tuberculosis and lung cancer separately, which is helpful for readers to understand the context of the study.

Comment 1: *However, there is a lack of explanation why tuberculosis is especially important for lung cancer risk. Please further elaborate the potential policy or clinical relevance between these two diseases.*

Reply 1: Thanks. We have modified our text as advised, and clinical relevance between carcinogenic infections, which tuberculosis is included in, and lung cancer was added in line 49-50 and 58-62. We think the added content in the introduction section can reinforce the connection between tuberculosis and lung cancer risk.

Changes in the text: Some information and two references were added in line 49-50 and 58-62.

Comment 2: *In the introduction section, what are the potential screening or intervention given that tuberculosis is associated with an increased lung cancer risk?*

Reply 2: Thanks for your advice. We added some information with a reference in line 58-62, these added content with the addition of existing information line 63-66 can associate tuberculosis with an increased lung cancer risk.

Changes in the text: The content was added in line 58-62.

Comment 3: *Does the association of tuberculosis with lung cancer differ between active and latent tuberculosis? Please further elaborate in the manuscript.*

Reply 3: Both latent tuberculosis infection and active tuberculosis were reported to increase the lung cancer incidences. We added this content in section "2. Epidemiology correlations between TB and LC" in line 97-98.

Changes in the text: The content was added in line 97-98.

Comment 4: *Line 78-80, those information are more relevant to the introduction section. Are there specific reasons to mention India and China in this section?*

Reply 4: There were no particular reasons to mention India and China, we just wanted to introduce the general incidence of tuberculosis in the world here.

Changes in the text: To make it clear, we have modified our text to "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" in line 72-73.

Comment 5: *Line 89-101, the references 15 and 16 are not the most updated meta-analysis on the association between tuberculosis and lung cancer. The reference 21 reported the results of meta-analysis in 2020. Please consider including the latest evidence. Author may also consider incorporating the information on population attributable fraction.*

Reply 5: Thanks for your kindly remind. "References 15 and 16" are really not the most updated meta-analyses, so we have modified our text as advised, the "reference 21" was added in this section. Incorporating the information on population attributable fraction is a good advice for us, but we found no relevant literatures about population attributable fraction in tuberculosis-related lung cancers on PubMed for us to cite, and we think the focus of this review was the molecular mechanism and possible interactions between lung cancer and tuberculosis, and so we decided not to include the population attributable fraction information.

Changes in the text: The "reference 21" (now it's ref. 9) was added in line 95-97.

Reviewer B

Lung cancer is a known risk factor for developing active tuberculosis, whereas it is controversial whether tuberculosis is a risk factor for lung cancer. The present study reviewed the association between lung cancer and tuberculosis. Overall, the review is well performed, however, there are potential limitations in this study.

Comment 6: *First, the author should discuss the cause of tuberculosis progression during ICIs therapy. Several studies revealed active tuberculosis in patients undergoing ICIs therapy (Fujita K, et al. J Thorac Oncol. 2016). Conversely, improvement of pulmonary NTM in a lung cancer patient treated by ICIs has been reported (Ishii S, et al. Inten Med. 2018). ICIs therapies seem to be positive and negative effect in patients with mycobacterium infection.*

Reply 6: Thanks for your advice. These two literatures are really needed for our article, so we put it in our review in section "6. The occurrence of TB during anti-PD-1/PD-L1 therapy"

Changes in the text: The added information "A case report[97] showed nivolumab (an anti–PD-1antibody immune checkpoint inhibitor) treatment promotes the progression of *Mycobacterium abscessus* disease. In addition, Fujita et al.[98] reported a patient with squamous cell lung cancer developed bacteriologically confirmed acute pulmonary TB after eight cycles of nivolumab administration." is in line 304-309.

Comment 7: *Second, there was no reference article in line 249-251.*

Reply 7: Sorry for our carelessness, the missing reference was added.

Changes in the text: The missing reference was added in line 255 as ref. 87.

Reviewer C

Comment 8: *Xiong et al., reviewed the field of tuberculosis and lung cancer, more focused on how macrophages phenotype changes the local environment and increases the risk of lung cancer.*

Reply 10: We have modified our text as advised. Some information about how macrophages phenotype changes the local environment and increases the risk of lung cancer were added in section "4. M2 polarization of macrophages induced by *Mtb* may lead to LC".
Changes in the text: The added information were in line 211-212 and line 226-233.

Comment 9: *Also the figures included in this review needs more interpretation in the text. it looks like a catalog of information with references but they failed to incorporate the information provided in the figures. In many places the connectivity of the information is missing.*

Reply 9: Thanks for your advice. After careful examination, we found some contents in Figure 1 was missing. Figure 1 is a summary of chapter 3 in the manuscript: Mechanisms of chronic inflammation elicited by *Mtb* infection in tumorigenesis. We have carefully compared and supplemented the contents and illustrations in the manuscript and Fig.1 and rearranged them.
Changes in the text: see line 129-130, 132-133, 137-138, and 186 in manuscript and Fig 1. Legend.

Reviewer D

This review article thoroughly described the relationship between lung cancer and pulmonary tuberculosis. The authors tried to demonstrated the mechanism and evidences of their close relationship. They covered many interesting topics with EGFR, Immunotherapy, and BCG.

I think the structure and figures of this article is good.

minor comments
Comment 10: *fig 1. legend: LC is also can develop --> LC also can develop*
Reply 10: Sorry for our carelessness, we have modified our text as advised (see Fig 1. legend)
Changes in the text: The redundant word "is" was deleted in Fig 1. Legend.