Editorial

How Tuberculosis Scar Could Induce Lung Cancer?

Elvando Tunggul Mauliate Simatupang, Arya Marganda Simanjutak, Indra Yovi, Rohani Lasmaria Simbolon, Sri Melati Munir, Dewi Wijaya

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Riau, Pekanbaru, Riau

Introduction

In 2022, there will be 10.6 million cases of tuberculosis, which is a serious problem worldwide. Thailand's cohort research after the COVID-19 pandemic found a 7-fold risk of tuberculosis infection in COVID-19 patients, pointing to a probable rise in TB cases. In order to completely eradicate TB, care must be given to patients both before and after infection, guaranteeing public health against TB infection.[1,2]

Scanchez, et al.'s[3] 2022 meta-analysis, TB patients have a 1.5 times higher chance of developing lung cancer, and this risk continues to rise for two years following diagnosis. Given that the pathomechanism is still up for discussion, understanding the risk's mechanism is essential. The goal of this literature review is to provide readers a thorough grasp of the relationship between lung cancer and TB.

Pathogenesis of Pulmonary TB

A chronic infection called pulmonary tuberculosis (PTB) is distinguished by a longer infectious phase and remodeling of the lung parenchyma. Granulomas produced by Mycobatecterium tuberculosis (Mtb) germs, myeloid cells, and lymphocyte cells are examples of pathological changes. In response to inhaling Mtb, both the innate immune system and the adaptive immune system are activated, with the innate immune system causing macrophages to phagocytose Mtb. The capacity of macrophages to eradicate Mtb reaches a threshold limit as a result of this procedure. Solid granulomas are produced as a result of adaptive immunity being triggered by adaptor proteins, MHC-I, and MHC-I. Host risk factors affect how the immune system reacts to Mtb bacteria, which can result in infection reactivation and hematogenous or lymphogenous spread.[4,5]

Pulmonary TB Cytokines and Lung Cancer : A Relationship

Inflammation brought on by Mtb infection results in lung epithelial cell hyperplasia, metaplasia, and fibroblast aggregation. Lung cancer is brought on by this initial phase of carcinogenesis. Due to Mtb infection, the inflammatory cytokines INF-, IL-1, IL-2, IL-12, and TNF are produced, which causes a protracted inflammatory response in lung tissue.

Korespondensi: **Arya Marganda Simanjuntak**
E-mail: *arya.marganda@gmail.com*

Tumor formation is intimately associated with cell hyperplasia, apoptosis, and inflammatory chemicals including TLR-2 and IL-6.[6,7] Asthma, COPD, and lung cancer all exhibit chronic inflammation, which is influenced by the NF-B signaling pathway.Mtb infection has a major impact on the biocellular relationship between pulmonary TB and lung cancer, resulting in a cytokine storm that both hurts and promotes lung epithelial growth. Vascular Endothelial Growth Factor (VEGF) is released in large amounts by T-cells during active TB, which may result in hypervascularization and lung cancer.[8]

Effector MTB Proteins Against Cancer Development

The TNF-responsive p53 in the A549 cell line is targeted by Sonic Hedgehog (SHH) signaling, which is activated by Bacillus Calmette Guerin (BCG). Mtb prevents TNF-induced tumor clearance and boosts tumor growth, suppressing apoptosis and promoting tumorgenesis. A gene involved in cell division, cell death, and cell senescence called GADD45A can be prevented from being transcribed by the Mtb effector protein PtpA. Tumor cell proliferation can be accelerated by blocking eEF1A1 and Mce2E's K48-linked polyubiquitination.[9,10] When NOX4 is blocked, TB-related pleural effusion can hasten the formation of A549 cell cancer. Lung tumor cells were shown to have Mtb IS6110 DNA sequences, pointing to a connection between Mtb secreted protein elements and lung cancer. The synthesis of COP1, which targets and eliminates P53 and stops cell death, is increased by BCG. The Mtb fibrosis-affected tumor microenvironment is driven by NOX4-p62, whereas the PtpA protein encourages A549 cell proliferation and migration.[11]

Pulmonary TB Reactive Species Production to Avoid Carcinogenesis

When infected with Mtb, macrophages and alveolar epithelial cells create an excessive amount of reactive oxygen species (ROS) and nitric oxide (NO), with ROS serving as the primary weapon during phagocytosis.[12,13] During pulmonary fibrosis, ROS produced by inflammatory cells can damage mitochondrial DNA (mtDNA). ROS are released by damaged mitochondria and have the ability to oxidize proteins, lipids, and mtDNA. This damage sets off biological processes that lead to tissue damage, slower lesion repair, and fibrosis. These processes include DNA damage, mitochondrial dysfunction, apoptosis suppression, and signal transduction restrictions.[14–17] Danger Associated Molecular Patterns (DAMPS) and Idiopathic Pulmonary Fibrosis (IPF) are associated processes. Lung fibrosis results from the stimulation of fibroblasts and macrophages by mtDNA exposure. The formation of extracellular neutrophils, inflammation, and tissue remodeling are all influenced by mtDNA. Increased ROS release and mtDNA damage are the main characteristics, which promote oncogene expression and cell growth.[18,19] P21 expression is prevented by cell growth, which halts the G2/M cycle and mitotic progression. Through binding to cyclin-dependent kinases, it also prevents the transformation from G0 to G1 phase change and the transition from G1 to S phase. By accelerating cell division, lowering DNA damage and mutation, and cutting down on DNA repair time, these modifications could promote carcinogenesis.[20,21]

COX-2's part in Pulmonary Tuberculosis Carcinogenesis

Studies have shown that upregulation of prostaglandin E2/Cyclooxygenase-2 (PGE2/COX-2) is a contributing factor to bacterial, fungal, and viral infections. Macrophages infected with Mtb may promote PGE2/COX-2 signal transduction, which may reduce the immunological response and improve the survival and spread of Mtb.Peripheral blood tests for individuals with active TB show elevated levels of 22 MDSCs, and COX-2 inhibitors are being investigated for Host Directed Therapy (HDT) in patients with pulmonary TB. PGE2/COX-2 signal transduction activation is revealed by quantitative RT-PCR analysis and protein identification in Mycobacterium bovis and BCG patients.[23,24] Increased COX-2 and 5-LOX levels were seen in monocyte derivatives treated with Mtb-produced PPD, which promoted tumorgenesis by affecting MMP-9 activity and preventing cancer cell motility and invasion via Akt, NF-B, and AP-1 signaling pathways.[25,26] COX-2 overexpression inhibits apoptosis and increases the growth of intratumoral microvessels in addition to having an effect on tumor spread.[27] Lung TB raises the risk of lung cancer by causing more DNA damage, reducing apoptosis, encouraging cell proliferation, and enhancing angiogenesis through the COX-2 phenotype, which raises the level of BCL-2 and the risk of cancer.[28,29]

Conclusion

It is imperative to do research on the epidemiology and molecular biology of the association between pulmonary TB and lung cancer. Globally, each year there are around 2.09 million new instances of lung cancer, 10 million new cases of P-TB, and 10 million new cases of lung TB. Effective prevention and therapy depend on early and precise diagnosis. Chronic inflammation, unbalanced immune system regulation, and gene mutations brought on by extended TB processes are all risk factors for lung cancer development from pulmonary tuberculosis. Future research may be able to compare pulmonary TB and lung cancer thanks to a basic understanding of pathogenesis.

References

1. World Health Organization. Global Tuberculosis Report 2022. Geneva; 2022.
2. Kumwichar P, Chongsuvivatwong V. COVID-19 pneumonia and the subsequent risk of getting active pulmonary tuberculosis: a population-based dynamic cohort study using national insurance claims databases. EClinicalMedicine [Internet]. 2023;56:101825. Available from: https://doi.org/10.1016/j.eclinm.2023.101825
3. Cabrera-Sanchez J, Cuba V, Vega V, Van der Stuyft P, Otero L. Lung cancer occurrence after an episode of tuberculosis: a systematic review and meta-analysis. Eur Respir Rev. 2022 Sep 30;31(165).
4. Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GAW. Lung remodeling in pulmonary tuberculosis. Journal of Infectious Diseases. 2005;192(7):1201–10.
5. Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GAW. Lung remodeling in pulmonary tuberculosis. J Infect Dis. 2005 Oct 1;192(7):1201–9.
6. Wang J, Ge P, Qiang L, Tian F, Zhao D, Chai Q, et al. The mycobacterial phosphatase PtpA regulates the expression of host genes and promotes cell proliferation. Nat Commun. 2017 Aug 15;8(1):244.
7. Holla S, Ghorpade DS, Singh V, Bansal K, Balaji KN. Mycobacterium bovis BCG promotes tumor cell survival from tumor necrosis factor-α-induced apoptosis. Mol Cancer. 2014 Sep 11;13:210.
8. Woo SJ, Kim Y, Jung H, Lee JJ, Hong JY. Tuberculous Fibrosis Enhances Tumorigenic Potential via the NOX4-Autophagy Axis. Cancers (Basel). 2021 Feb 8;13(4).
9. Dagaonkar RS, Choong C V, Asmat AB, Ahmed DBA, Chopra A, Lim AYH, et al. Significance of coexistent granulomatous inflammation and lung cancer. J Clin Pathol. 2017 Apr;70(4):337–41.
10. Königshoff M. Lung cancer in pulmonary fibrosis: tales of epithelial cell plasticity. Respiration. 2011;81(5):353–8.
11. Cooper AM, Khader SA. The role of cytokines in the initiation, expansion, and control of cellular immunity to tuberculosis. Immunol Rev. 2008 Dec;226:191–204.
12. Kwiatkowska S, Szkudlarek U, Luczyńska M, Nowak D, Zieba M. Elevated exhalation of hydrogen peroxide and circulating IL-18 in patients with pulmonary tuberculosis. Respir Med. 2007 Mar;101(3):574–80.
13. Zhang RR, Meng NN, Liu C, Li KL, Wang MX, Lv ZB, et al. PDB-1 from Potentilla discolor Bunge induces apoptosis and autophagy by downregulating the PI3K/Akt/mTOR signaling pathway in A549 cells. Biomed Pharmacother. 2020 Sep;129:110378.
14. Bocchino M, Agnese S, Fagone E, Svegliati S, Grieco D, Vancheri C, et al. Reactive oxygen species are required for maintenance and differentiation of primary lung fibroblasts in idiopathic pulmonary fibrosis. PLoS One. 2010 Nov 16;5(11):e14003.
15. Agrawal A, Mabalirajan U. Rejuvenating cellular respiration for optimizing respiratory function: targeting mitochondria. Am J Physiol Lung Cell Mol Physiol. 2016 Jan 15;310(2):L103-13.
16. Kim SJ, Cheresh P, Jablonski RP, Williams DB, Kamp DW. The Role of Mitochondrial DNA in Mediating Alveolar Epithelial Cell Apoptosis and Pulmonary Fibrosis. Int J Mol Sci. 2015 Sep 7;16(9):21486–519.
17. Schumacker PT, Gillespie MN, Nakahira K, Choi AMK, Crouser ED, Piantadosi CA, et al. Mitochondria in lung biology and pathology: more than just a powerhouse. Am J Physiol Lung Cell Mol Physiol. 2014 Jun 1;306(11):L962-74.
18. Boyle WJ, Smeal T, Defize LH, Angel P, Woodgett JR, Karin M, et al. Activation of protein kinase C decreases phosphorylation of c-Jun at sites that negatively regulate its DNA-binding activity. Cell. 1991 Feb 8;64(3):573–84.
19. Meyer M, Pahl HL, Baeuerle PA. Regulation of the transcription factors NF-kappa

B and AP-1 by redox changes. Chem Biol Interact. 1994 Jun;91(2–3):91–100.
20. Gupta S, Hussain T, Mukhtar H. Molecular pathway for (-)-epigallocatechin-3-gallate-induced cell cycle arrest and apoptosis of human prostate carcinoma cells. Arch Biochem Biophys. 2003 Feb 1;410(1):177–85.
21. Deng Y, Liu B, Mao W, Shen Y, Fu C, Gao L, et al. Regulatory roles of PGE2 in LPS-induced tissue damage in bovine endometrial explants. Eur J Pharmacol. 2019 Jun 5;852:207–17.
22. Martínez-Colón GJ, Moore BB. Prostaglandin E2 as a Regulator of Immunity to Pathogens. Pharmacol Ther. 2018 May;185:135–46.
23. Jøntvedt Jørgensen M, Jenum S, Tonby K, Mortensen R, Walzl G, Du Plessis N, et al. Monocytic myeloid-derived suppressor cells reflect tuberculosis severity and are influenced by cyclooxygenase-2 inhibitors. J Leukoc Biol. 2021 Jul;110(1):177–86.
24. Liu H, Xiong X, Zhai W, Zhu T, Zhu X, Zhu Y, et al. Upregulation of Cytokines and Differentiation of Th17 and Treg by Dendritic Cells: Central Role of Prostaglandin E2 Induced by Mycobacterium bovis. Microorganisms. 2020 Jan 31;8(2).
25. Nore KG, Jørgensen MJ, Dyrhol-Riise AM, Jenum S, Tonby K. Elevated Levels of Anti-Inflammatory Eicosanoids and Monocyte Heterogeneity in Mycobacterium tuberculosis Infection and Disease. Front Immunol. 2020;11:579849.
26. Pintha K, Chaiwangyen W, Yodkeeree S, Suttajit M, Tantipaiboonwong P. Suppressive Effects of Rosmarinic Acid Rich Fraction from Perilla on Oxidative Stress, Inflammation and Metastasis Ability in A549 Cells Exposed to PM via C-Jun, P-65-Nf-Kb and Akt Signaling Pathways. Biomolecules. 2021 Jul 23;11(8).
27. Fosslien E. Biochemistry of cyclooxygenase (COX)-2 inhibitors and molecular pathology of COX-2 in neoplasia. Crit Rev Clin Lab Sci. 2000 Oct;37(5):431–502.
28. Kase S, Osaki M, Honjo S, Adachi H, Tsujitani S, Kaibara N, et al. Expression of cyclo-oxygenase-2 is correlated with high intratumoral microvessel density and low apoptotic index in human esophageal squamous cell carcinomas. Virchows Arch. 2003 Feb;442(2):129–35.
29. Fosslien E. Review: molecular pathology of cyclooxygenase-2 in cancer-induced angiogenesis. Ann Clin Lab Sci. 2001 Oct;31(4):325–48.