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OBM Genetics

Review

Mycobacterium Tubercular Mediated Inflammation and Lung Carcinogenesis: Connecting Links

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Academic Editor: Xiangzi Han

Special Issue: Pharmacogenomics in Drug Development

OBM Genetics
2023, volume 7, issue 2
doi:10.21926/obm.genet.2302183

Received: September 03, 2022
Accepted: June 12, 2023
Published: June 21, 2023

Abstract

Lung cancer is a leading cause of death among all the cancer worldwide and it has the highest occurrence and mortality rates. *Mycobacterium tuberculosis* (MTB) induced tuberculosis has been known as one of the risk factors for lung carcinogenesis. The exact mechanism of MTB is understood to date. Several research and epidemiological studies about the link between tuberculosis and lung cancer exist. It has been proposed that tuberculosis causes chronic inflammation, which increases the risk of lung cancer by creating a favorable environment. EGFR downstream signaling promotes constitutive activation of TKIs domain due to the mutation in exon 19 and exon 21 (L858R point mutation), which leads to cell proliferation, invasion, metastasis, and angiogenesis, causing lung adenocarcinoma. Several other studies have shown that human monocyte cells infected by MTB enhance the invasion and cause induction of epithelial-mesenchymal transition (EMT) characteristics in lung cancer cell co-culture. This review article has tried to draw a relationship between chronic tuberculosis and lung carcinogenesis.

Keywords

Risk factors; Mycobacterium tuberculosis; inflammation; lung cancer

1. Introduction

Lung cancer is a heterogeneous type of cancer that become the leading cause of death worldwide [1, 2]. In 2020, 2.2 million new lung cancer cases were reported, accounting for 11.4% of all the cancers and 1.8 million deaths contributing to 18% of all carcinogenic deaths [3]. In India, 0.068 million new lung cancers cases and 0.064 million deaths were reported, accounting for 5.9% and 8.1% of all the newly diagnosed cancers and cancers-related deaths, respectively [1]. It has been proved that tuberculosis has been linked with increased lung cancer risk through various mechanisms like chronic pulmonary inflammation and fibrosis [4, 5]. Tuberculosis is a bacterium-generated disease mainly caused by *Mycobacterium tuberculosis* (MTB). It is estimated that 6% of the deaths of all the deaths are occurred due to tuberculosis per year worldwide and nearly 1.5 million people have died annually [6-8]. In India, according to the India TB Report 2020, more than 2.4 million tuberculosis cases were identified, and 0.08 million deaths occurred in 2019 [7, 9].

The literature revealed that MTB-mediated lung infection had been recognized as a potential contributing factor to the etiology of lung cancer [10-13]. Substantial and prolonged pulmonary inflammation due to MTB raises the risk of lung cancer. Such prolonged inflammation leads to host tissue damage, fibrosis, scar formation, and genetic alterations; therefore, these changes may be one of the reasons causing lung cancer [14-17]. It has been noticed that lung cancer risk was higher in tuberculosis (TB) patients after 2 years of TB diagnosis. Similarly, a meta-analysis study reported that TB might be associated with a 1.7-fold rise in the risk of lung cancer [18]. It is quite possible that MTB infection damages the lungs and subsequently increases lung cancer risk. But in most cases during the tubercular diagnosis, the prognosis/diagnosis for initiating lung cancer gets skipped [2]. However, the link between the exact molecular biology of *Mycobacterium tuberculosis* to increased lung cancer risk is yet to be determined. Literature reveals a strong possibility of a connection between tuberculosis and lung cancer development [4].

2. Mycobacterium Tubercular Pathogenesis

2.1 Mycobacterium Tuberculosis

Mycobacterium is a rod-shaped and non-motile bacterium that belongs to the *Mycobacteriaceae* family and it infects the lungs and causes TB [5, 19]. The MTB consists of two layers (outer and inner layer) that occupy the plasma membrane. The lipid-linked polysaccharides such as mannose-capped lipoarabinomannan (LAM), lipo manna, and sulfolipids are found in the outer and inner layers [19, 20]. Lipids and proteins in the outer layer of MTB are considered effector molecules. Peptidoglycans, arabinogalactan and mycolic acids are covalently linked with each other and present in the inner layer (Figure 1) [21, 22]. The presence of mycolic acid and mannose is essential for TB pathogenesis. Various researchers have reported numerous biological processes linked to mycolic acids. Due to their poor permeability, mycolic acids create a tight hydrophobic barrier known as the biomembrane that functions as a physical defense and fortification against the hostile environment inside macrophages and antibiotics. Additionally, mycolic acids are involved in host-pathogen

interactions and are also connected to MTB virulence [23]. The more virulent strain of MTB serves a significant role in the disease development, as it has more transmissibility, leading to higher morbidity and death rate in patients with lungs infection [19]. A characteristic feature of virulent strains of MTB is the presence of a cord factor (trehalose 6, 6'-dimycolate; TDM) on their cell surface. The main function of TDM is to inhibit fusion between phagosome and lysosome. This process is accomplished by trehalose which causes hindrance in fusion by increasing hydration force and causing steric restraints. This inhibition of fusion leads to the escape of MTB from host defense mechanisms and hence, transmissibility increases [24].

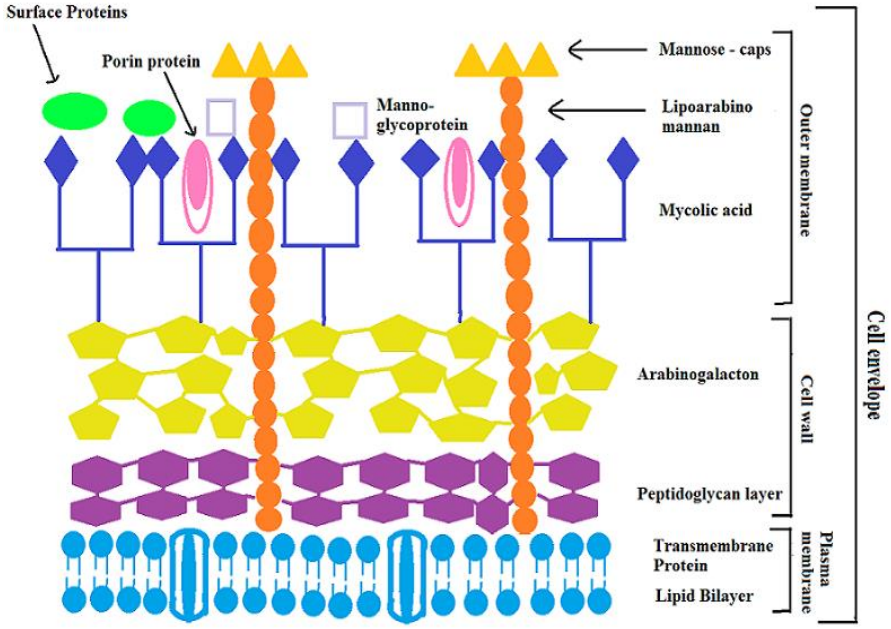

Figure 1 Schematic representation of MTB cell wall. Plasma membrane contains transmembrane protein and lipid bilayer, Cell wall contains peptidoglycan layer and arabinogalactan, and outer membrane contains mycolic acids, porin and other surface proteins. Lipoarabinomannan (Mannose-capped) is found in entire cell wall and outer membrane.

2.2 Pathogenesis of Tuberculosis

The *Mycobacterium tuberculosis* enters the lungs by aerosol transmission and adheres to the epithelium (a lining of epithelial cells) and reaches into the alveoli [19]. In the initial encounter, alveolar macrophage interacts with the pathogen in numerous ways such as binding between mannose (present on the surface of MTB) and mannose receptors (present on the macrophages), binding between complement binding receptors and c3b protein and binding with pathogens via pattern recognition receptors (PRRs) (Figure 2) [5, 20, 25, 26]. In normal circumstances, the macrophage capture the MTB by the above-discussed binding mechanism and degrades the MTB by phagosome-lysosome fusion (Figure 2) [27]. But in diseased conditions, MTB alters the pH of the phagosome and prevents several protein activations that allow phagosome-lysosome fusion [5, 28, 29]. But macrophage cells get activated and release the nitric oxide, reactive oxygen species and chemokines/chemo-attractants that lead to the activation of monocytes, T-cells, B-cells, and numerous other types of inflammatory cells. Resulted, the activation of inflammatory immune

components and the presence of nitric oxide and reactive oxygen species leads to damage to lung tissues that cause the release of fatty acids in large amount; therefore, these changes cause the infected area to become more acidic and create the hypoxia condition that raises the risk of lung cancer [7, 29-31].

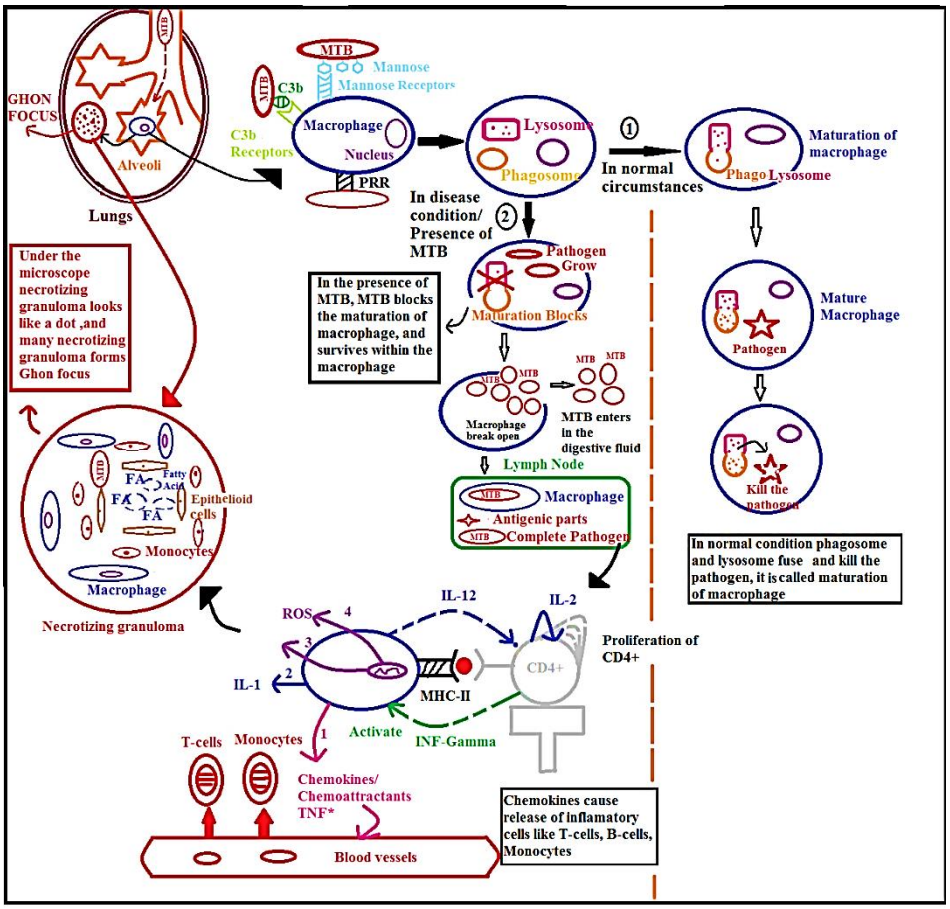

Figure 2 Molecular pathogenesis of tuberculosis. MTB, *Mycobacterium tuberculosis*; C3b, Complement component 3; PRR, Pattern recognition receptors; IL-2, Interleukin-2; IL-12, Interleukin-12; IL-1, Interleukin-1; $CD4^+$, Cluster of differentiation 4; MHC-II, Major histocompatibility complex class II; INF-γ, Interferon-gamma; NO, Nitric oxide; ROS, Reactive oxygen species; TNF, Tumor necrosis factor; FA, Fatty acids.

3. Risk Factors and Pathophysiology of Lung Cancer

Certain hallmarks of carcinogenesis include growth signals, inactivity of antigrowth signals, dodging of apoptosis, unlimited replication, support angiogenesis, and metastasis, leading to individual cells or groups of cells acquiring capabilities that allow them to convert into a malignant entity. The mechanism that allows these changes leads to instability of the genome and loss of DNA repair ability. Genetic, behavioral, and environmental factors affect this process, which can lead to the risk of an individual developing lung cancer [32]. The prevalence of indoor air contaminants, the usage of household and biomass sources, the absence of nutrients in our diet, industrial susceptibility, and the potential increase in communicable diseases such as MTB in the Indian subcontinent, and smoking tobacco, both cigarettes and beedis are a significant risk factor for lung cancer in Indian men and women [33]. The pathophysiology of lung carcinoma is not entirely known.

Hypothetically, cigarette smoking leads to dysplasia in lung epithelium tissue due to continuous exposure to carcinogens prevalent in cigarettes/tobacco. This repeated exposure promotes mutation, affects protein synthesis, disrupts the cell cycle, and hence, promotes carcinogenesis. The proto-oncogenes are normal genes involved in cellular growth and proliferation but also play a crucial role in carcinogenesis. In the two different histologically divided lung cancers, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), different proto-oncogenes gets mutated genetically and lead to lung carcinoma progression. The genetic alteration in the most prevalent proto-oncogenes such as MYC, BCL2, and p53 have been linked to lung cancer development in SCLC and the genetic mutation in EGFR, KRAS, and p16 proto-oncogenes are co-related to lung cancer progression in NSCLC [34].

4. Mycobacterium Tuberculosis Induced Inflammation Related Pathways in Lung Cancer

Previously it has been suggested that pulmonary tuberculosis leads to a high risk of lung cancer but the exact mechanism inter-linking these two diseases is not identified. Literature indicates that tuberculosis is linked to an increased lung cancer risk [35]. Persistent inflammation for an extended period leads to an imbalance in DNA damage and repair mechanism, which may be possible pathophysiology of lung carcinoma in TB patients. An experiment showed that chronic respiratory inflammation induced lung cancer in a KRAS-mutated mouse model [36]. Also, a significant clinical investigation tells that acute and chronic inflammatory response promotes tumor development and progression by various mechanisms. Another linking fact is that chronic pulmonary tuberculosis infection results in dysplasia and carcinoma of squamous epithelium in the lung following genomic alteration and growth factor dysregulation.

During active TB in granulomas, various inflammatory responses get generated against MTB that damages the tissue. In the damaged tissue, MTB triggers the release of inflammatory factors such as TNF, INF-γ, IL-1, IL-2, and IL-12, causing inflammation in lung epithelial tissue. Tissue repairing is mediated by high activity of fibroblast which produces extracellular matrix (ECM) components and fibrosis. That may lead to the progression of lung cancer by producing TGF-β, IL-4, IL-3, and IL-13. IL-4 is a proinflammatory cytokine and its production promotes cancer cell proliferation, apoptotic resistance, and metastatic potential. IL-3 act as a growth factor and it might be possible that the production of this interleukin promotes the growth of cancer cells in the tumor microenvironment. IL-13 mediates numerous effects on various immune cells, endothelial cells, and fibroblasts and suppresses the anti-tumor immune response that leads to the generation of cancer cells [37-42]. Some pro-inflammatory cytokines like TNF and IL-6 cause changes in the epithelial cells to up-regulate the synthesis of the anti-apoptotic gene by the NF-κB pathway. The tissue repair process leads to cellular proliferation and angiogenesis, creating a suitable environment for tumor progression [7].

4.1 Transforming Growth Factor-Beta (TGF-β) Signaling and Mycobacterium Tuberculosis-Induced Inflammation

The TGF-β ligands (TGF-β 1, TGF-β 2, and TGF-β 3) are members of the cytokines family, which control different cellular functions like proliferation, survival, differentiation, and migration [28]. TGF-β regulates two types of activities in cancer disease. First, it plays a vital role in cancer invasion, angiogenesis, and metastasis by acting as a tumor promoter in carcinoma cells. This function of TGF-

β is due to various mutations in TGF-β ligands, its receptors and in SMAD2 and SMAD4, ultimately leading to pre-malignant cells' transition to cancerous phenotype [38]. Secondly, it regulates anti-tumor activities by suppressing the tumor in pre-malignant cells [36]. TGF-β does tumor suppression by inhibiting proliferation and promoting apoptosis via upregulating the expression of cyclin-dependent kinase (CDK) inhibitors and downregulating MYC expression [38]. Several studies show that the TGF-β signaling pathway is actively involved in pulmonary fibrosis and plays a vital role in MTB-induced inflammation of lung tissue. Studies found the higher expression of TGF-β, SMAD3, SMAD4, and connective tissue growth factor (CTGF) and hence, reported the connection between transcriptional and epigenetic processes in TGF-β mediated pulmonary fibrosis which in turn, leads to lung cancer [39]. The detailed mechanism of the TGF-β pathway mediated inflammation and cancer hallmark is depicted in Figure 3 [43-46].

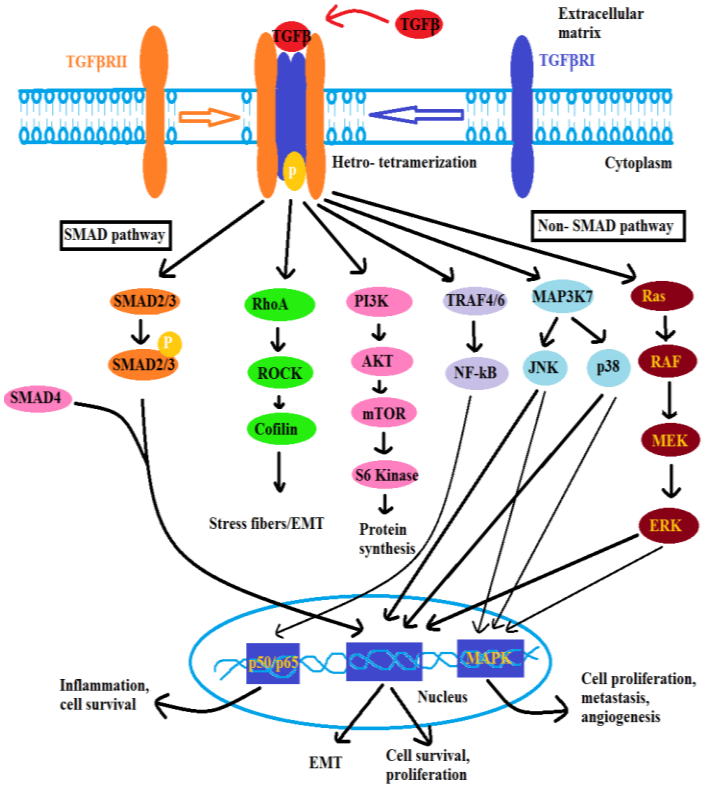

Figure 3 TGF-β signaling, inflammation and cancer hallmarks. Activation of SMAD based TGF-β pathway leads to activation of cell survival and epithelial to mesenchymal transition genes which helps in sustainability of cancer hallmarks like cellular proliferation, cell survival and epithelial to mesenchymal process. Activation of non-SMAD based TGF-β pathways activate NF-κB (p50 and p65) and MAPK signaling pathways that cause the inflammation and raise the sustainability of cancer cell proliferation, their survival, angiogenesis, and metastasis. Abbreviation; TGF-β, Transforming growth factor-beta; RhoA, Ras homolog family member A/Rho –like GTPase; TRAF4/6, TNF receptor-associated factor 4/6; PI3k, Phosphoinosotide 3-kinase; AKT, Serine/threonine-specific protein kinase; mTOR, Mammalian target of rapamycin; MAP3K7, Mitogen-activated protein kinase kinase 7; JNK, c-Jun N-terminal kinase; RAF, Rapidly Accelerated Fibrosarcoma; MEK, Ras/Raf/Mitogen-activated protein kinase/ERK kinase; ERK, Extracellular-signal-regulated kinase.

4.2 NF-κB Signaling and Mycobacterium Tuberculosis Induced Inflammation

NF-κB is a heterodimer of two proteins (RelA and p50). It is a transcription factor that has an inducible activity. Its active form regulates different genes involved in inflammation, cell proliferation, metastasis, invasion, and apoptosis; synthesis of inflammatory cytokines and chemokines, and morphogenesis [45]. Chronic inflammation due to MTB leads to the release of different inflammatory and pro-inflammatory cytokines like TNF and IL-6, which causes changes in the epithelial cells to upregulate the expression of the anti-apoptotic gene by the NF-κB pathway [7]. NF-κB regulates different cellular functions by two types of pathways-canonical and non-canonical. Through the canonical pathway, ligands activate different receptors such as cytokine receptors, T-cell receptors (TCRs), tumor necrosis factor receptors (TNFR), pattern recognition receptors (PRRs), and B-cell receptors (BCRs). Activation of receptors phosphorylates the inhibitory factor IκB-α by a multi-subunit IκB kinase (IKK) and leads to inducible degradation of IκB-α. Activated IKK leads to ubiquitin-dependent degradation of the IκB-α factor in the proteasome. Now RelA and p50 complex is free to move in the nucleus. It binds to the κB site and regulates different kinds of cellular functions. Non-canonical signaling does not regulate the degradation of IκB-α, but it leads to the synthesis of NF-κB2 precursor protein (p100). This helps the degradation of IκB-α (Figure 4) [47-50].

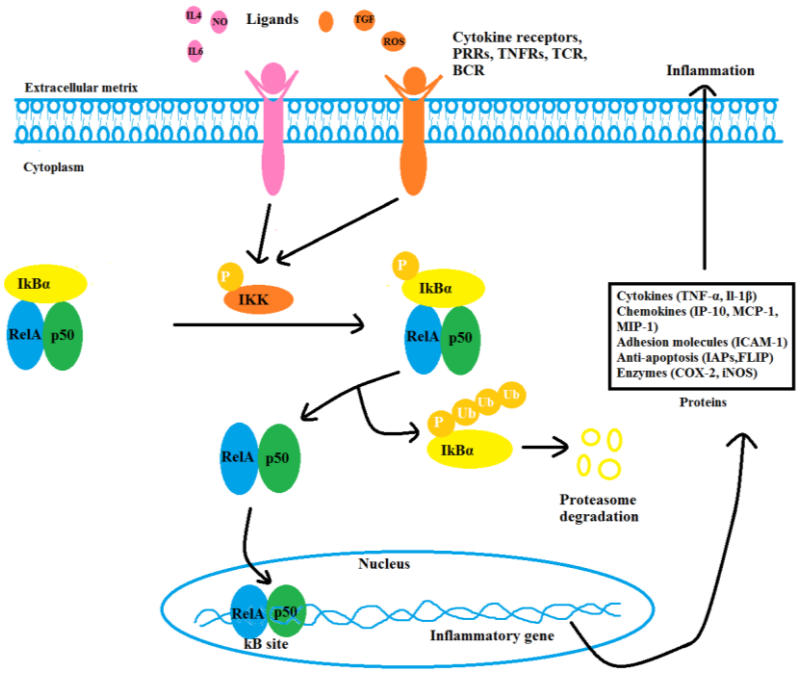

Figure 4 NF-κB signaling pathway and inflammation. Different inflammatory ligands activate receptors (cytokine receptors, PRRs, TNFRs, TCR, and BCR) which phosphorylate the IKK triggering the ubiquitin dependent degradation of NF-κB inhibitor protein IκB-α. Now, RelA and p50 complex moves into the nucleus and regulate cellular function. Abbreviation; PRRs, Pattern recognition receptors; TNFRs, Tumor necrosis factor receptors; TCR, T-cell receptors; BCR, B-cell receptors; IκB-α, Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IKK, IκB kinase.

5. EGFR Mutation in Tuberculosis and Lung Cancer

The EGFR gene, which encodes signaling proteins crucial for the survival and proliferation of the cell, leads to significant mutations occurring in lung adenocarcinoma when mutated [51]. EGFR regulates several oncogenic functions like cell proliferation, survival, differentiation, angiogenesis, invasion, and metastasis. Hence, EGFR mutations cause the development of several cancers, including lung cancer. EGFR leads to the coding of transmembrane tyrosine kinase receptors. The activation of EGFR mutations leads to tyrosine kinase activation and oncogenic transformation of lung epithelial cells *in vitro*. Multiple lung adenocarcinomas were developed in a transgenic rat model with inducible expression of the most frequent EGFR mutations sensitive to small-molecule inhibition. When ligand EGF binds to a receptor, the receptor homo or hetero dimerization occurs, leading to the tyrosine kinase domain phosphorylation. EGFR triggers signal transduction. Signal transduces by transcription factors such as PI3K/AKT/mTOR, RAS/RAF/MAPK, and JAK/STAT. Additional EGFR signaling pathways include enhanced protein expression or gene copy number (Figure 5) [52].

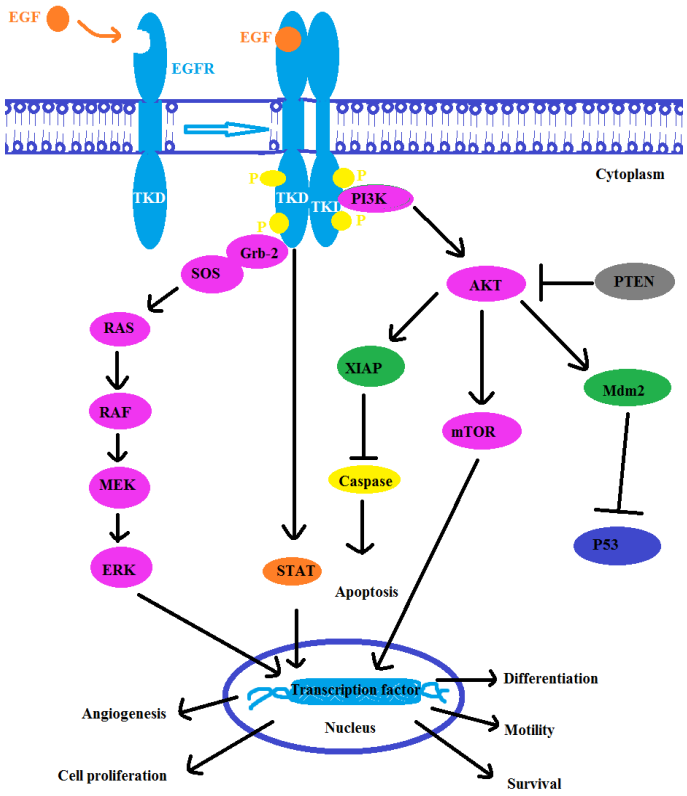

Figure 5 Epidermal growth factor signaling and cancer hallmarks. EGF-EGFR interaction leads to homo/hetero dimerization of tyrosine kinase domain which becomes activated after its auto-phosphorylation and ultimately starts downstream signaling by Grb2 and PI3k and modulates cancer hallmarks. Abbreviation; EGFR, Epidermal growth factor receptor; EGF, Epidermal growth factor; TKD, Tyrosine kinase domain; Grb2; Growth factor receptor-bound protein 2; RAF, v-raf murine leukemia viral oncogene homologs; ERK, Extra-cytoplasmic-regulated kinase, STAT, Signal transducer and activator of transcription; PI3K, Phosphatidylinositol-3-kinase; mTOR, Mammalian target of rapamycin; PTEN, Phosphate and tensin homolog.

There are several types of mutation in lung cancer, where EGFR mutation occurs in the first four exons of the intracellular tyrosine kinase domain. Among these, frame deletion on exon 19 has almost 20 variants that occur in nearly 45% of cases [53]. The most common variant of this is delE746-A750. A further common EGFR mutation is a missense mutation (L858R is the most common), which is a single nucleotide point mutation in exon 21, leading to a single amino acids change at codon 858, from leucine to arginine [54]. Mutation at the tyrosine kinase domain leads to structural changes, destabilization, and constitutive activation of domain kinase activity and triggers the activation of downstream signaling pathways [55]. It has been reported that 30 to 40% of Asian and nearly 15% of white patients with lung adenocarcinoma have EGFR mutation in their genome. In lung adenocarcinoma patients, deleting exon 19 and L858R point mutation in exon 21 is a significant gene alteration. The tumor caused by this mutation, when treated with EGFR tyrosine kinase inhibitors (TKIs), showed a dramatic response up to 73 to 91% and a more prolonged progression-free survival (PFS) up to 7.7 to 13.3 months [56]. It has been suggested that activating the EGFR gene in a human bronchial epithelial cell is induced by oxidant-induced goblet cell metaplasia. Also, overexpression of epiregulin induced by chronic tuberculosis is associated with invasiveness and the proliferation of EGFR-mutated cells [57]. In a study linking pulmonary adenocarcinoma in patients with old TB lesions and the non-TB group, it was seen that among 513 patients with lung adenocarcinoma, 21% had old TB lesions. 39% of patients had EGFR mutated tumors, of which 50% had a deletion in exon 19, and 43% had L858R point mutation. The frequency of EGFR mutation was higher in the old TB lesion group than in the non-TB group. The report has concluded that patients with old TB lesions were independently associated with a higher risk of EGFR mutation. This further demonstrated that chronic TB lesions are significantly related to an increased rate of EGFR mutation, among which primarily mutation is due to exon 19 deletion in lung adenocarcinoma patients. These studies draw a relationship between pulmonary tuberculosis and EGFR-mutated lung adenocarcinoma. However, more studies and investigations are required to draw parallels between increased mutation rates in pulmonary TB and its role in lung cancer patients [58].

6. Mycobacterium Tuberculosis and Lung Cancer Invasion/Metastasis

The chronic infection of MTB provides a conducive microenvironment for the induction of tumorigenesis, tumor progression, and metastasis by causing oxidative stress, producing inflammatory cytokines, and activating the toll-like receptors (TLRs) [59]. MTB infection causes releases of various cytokines such as INF-γ, IL-1, IL-2, IL-12, and TNF, which are responsible for causing lung tissue inflammation [59]. These inflammatory molecules overexpress anti-apoptotic pathways via NF-κB signaling, which in turn, plays a crucial role in metastasis and tumor advancement. Thus, it can be deduced that MTB infection can play a major role in tumor progression through NF-κB signaling mediated by inflammatory cytokines [60]. Several recent studies showed that human monocyte cell line THP-1 infected by MTB enhances the invasion and causes induction of EMT characteristics in lung cancer cell line A549 in co-culture. A549 cells, when cultured along with MTB-infected THP-1 cells, show molecular and morphological characteristics of EMT. Compared to separately cultured A549 cells, the co-cultured lung cancer cells show an enhanced expression of inflammatory cytokines like TNF-α, IL-1b, and IL-6 [61].

In tuberculosis, granulomas are formed, comprised of myeloid and lymphoid cells surrounding the MTB. The combination of *Mycobacterium* product and cytokines activates the macrophages, releasing reactive oxygen and reactive nitrogen species, prostaglandin inflammatory cytokines, and proteases. Accumulation of these chemicals and cytokines makes the microenvironment hostile to the bacteria. This inflammatory response plays a crucial role in tumor induction and metastasis stages. Fibroblast epithelial cells and macrophages are the non-malignant cells of the tumor microenvironment, influencing every aspect of metastasis. In the tumor microenvironment, tumor-mediated growth of the primary tumor and metastatic dissemination of the tumor to distant organs is facilitated by tumor-associated macrophages. Several stages of metastasis, like local invasion survival in the circulation extravasation and metastatic colonization, are related to the developmental process of epithelial-mesenchymal transition [61]. During EMT, tumor cells lose their epithelial cell characteristics such as loss of adherent junction, tight junction, and cell polarity. Further, they start showing mesenchymal characteristics like motility of cells and invasiveness. An increased expression of vimentin and N-cadherin and a decreased expression of E-cadherin, occludin, and claudin-7 leads to increase lung cancer cell migration and invasion on the onset of EMT [16]. EMT can be initiated by a cellular signal from the tumor microenvironment, commonly occurring at the tumor-stromal boundary of several invasive carcinomas. The tumor-derived signal recruit monocyte to develop into tumor-associated macrophages or TAMs [54]. TAM is a critical component of the tumor environment, which performs several significant functions promoting cell proliferation and angiogenesis, boosting the invasion by EMT induction, and playing a crucial role in inflammation and adaptive immunity. These TAMs secrete several pro-inflammatory cytokines required for inflammation-induced EMT, like TNF-α, IL-6, and IL-12. Bayle reported the correlation and coexistence of tuberculosis and lung cancer for the first time in 1810 by. This relationship between tuberculosis and lung carcinoma has become a significant clinical and pathological research field.

A report by Dacosta and Kinare, pathologists from KEM hospital India, has reported that in the patient with bronchogenic tumor, around 30-33% of lungs have shown active or healing TB lesions, compared to 7% in the general population. After this, several instances of the coexistence of tuberculosis and lung cancer have been reported, proving a mechanical relation between tuberculosis and lung carcinoma. Several expensive epidemiological studies have revealed the correlation between lung cancer and tuberculosis, but the cellular mechanism involved in this transition is yet to be understood [60].

7. Summary and Future Prospective

The epidemiological studies about pulmonary tuberculosis and lung cancer showed that a tuberculosis surge increases lung cancer risk through prolonged pulmonary inflammation and fibrosis. The prolonged pulmonary inflammation cause lung tissue damage and genomic alterations. Further repairing of damaged tissues cause pulmonary fibrosis and scaring, which is highly connected with the huge risk of lung cancer. Besides this, studies have shown that EGFR mutation rates are high in patients infected with chronic pulmonary tuberculosis. But how tuberculosis promoted the mutation and caused lung adenocarcinoma is unclear. The central hypothesis for linking pulmonary tuberculosis and lung cancer proposes chronic inflammatory responses during pulmonary tuberculosis promote the development and progression of lung adenocarcinoma by

forming a favorable environment, which leads to DNA mutation, cell proliferation, angiogenesis, differentiation, invasion, metastasis, survival, and motility. MTB can induce epithelial-mesenchymal transition and generate chronic inflammation, favorable for lung cancer development and progression. Researchers have several questions, such as "How should one answer the blockage of phagosome-lysosome fusion by MTB?" Many studies have been thrilled to reveal the mechanism blocking the phagosome and lysosome fusion, but the exact mechanism is still unclear. Correct information on the underlying mechanism will help design the drug to control TB-induced lung cancer. Another question arises: "How dies tuberculosis induce the EGFR mutation and cause lung adenocarcinoma?" Hence, knowing the underlying mechanism can be utilized for therapeutic purposes.

Acknowledgments

MS acknowledges financial support from the Indian Council of Medical Research, India in the form of ICMR-Senior Research fellowship [File No. 5/3/8/80/ITR-F/2020-ITR]. TB acknowledges DBT India for providing DBT-JRF fellowship. SK acknowledges DST, India for providing DST-FIST grant to the Department of Biochemistry, Central University of Punjab, Bathinda, India.

Author Contributions

SK supervised the study and wrote the manuscript. AV collected the data and prepared figures. MS helped in drafting and writing of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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