Tuberculosis and lung cancer

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Abstract

Objective. To describe the epidemiological studies about the relationship between lung cancer (LC) and pulmonary tuberculosis (Tb) and its possible molecular mechanisms. **Materials and methods.** We reviewed research databases in search of publications that included keywords LC and Tb. **Results.** It has been proposed that chronic inflammation in the lungs due to Tb could cause clastogenic activity in the DNA of bronchial epithelium. Another possibility is lateral gene transfer; since Mycobacterium tuberculosis (MTb) is an intracellular organism, bacterial DNA could integrate to bronchial epithelial cells inducing neoplastic transformation. **Conclusions.** There are epidemiological reports, particularly from Asian countries, which confirm a relationship between LC and Tb. MTb could play an active role in cellular transformation and it is important to elucidate the mechanism involved.

Keywords: tuberculosis; lung cancer; inflammation; EGFR; epidemiology

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Resumen

Objetivo. Describir los estudios que documentan la relación entre el cáncer de pulmón (CP) y la tuberculosis pulmonar (Tb) y sus posibles mecanismos moleculares. **Material y métodos.** Se revisaron bases de datos de publicaciones, usando como palabras clave CP y Tb. **Resultados.** Se ha propuesto que la inflamación crónica en el pulmón provocada por la Tb podría producir actividad clastogénica. Otra posibilidad es la transferencia lateral de genes; Mycobacterium tuberculosis (MTb) es un organismo intracelular facultativo cuyo DNA podría integrarse al material genético del epitelio bronquial induciendo transformación neoplásica. **Conclusión.** Existen evidencias epidemiológicas, particularmente en países asiáticos, que documentan la relación entre CP y Tb. MTb podría desempeñar un papel activo en la transformación neoplásica cuyo mecanismo debe de ser elucidado.

Palabras clave: tuberculosis; cáncer de pulmón; inflamación; EGFR; epidemiología

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Tuberculosis epidemiology and epidemiology link with lung cancer

Tuberculosis (Tb), caused by *Mycobacterium tuberculosis* (Mtb), is the main cause of death by an infectious agent with more than 1.8 million deaths per year, which makes Tb an important public health issue worldwide. It has been estimated that one third of the world population is a healthy carrier of Mtb (latent infection), from which approximately 10% will eventually develop active disease.[1] In México, there are more than 19 000 new cases per year, and in 2015 the incidence was three to 58.8 cases per 100 000 inhabitants, depending on the state.[2] Particularly in Asia there is strong epidemiological evidence indicating that Tb is associated with the development of lung cancer, particularly non-small cell adenocarcinoma, which is one of the most aggressive subtypes.

Lung cancer (LC) is the leading cause of cancer-related deaths in the world, in México most cases are diagnosed at a late stage and survival with traditional first-line chemotherapy platinum-based regimens is usually poor.[3,4] Non-small cellular lung cancer (NSCLC) accounts for approximately 85% of cases. The main subtypes are adenocarcinoma, squamous cell carcinoma and large cell carcinoma; cigarette smoking is causally related to lung cancer, accounting for approximately 85% of all patients in the United States and Europe, but only between 50-60% in México, particularly in terms of gender, the proportion decreases almost to 30% in women.[5,6]

There are several factors that participate in neoplastic transformation; being infected by a certain type of pathogen agent is one of these factors. The prevention and treatment of infectious agents have had a substantial effect on cancer prevention.[7] In 2008, about 16%, (around two million) of the new cancer cases that occurred worldwide were attributable to infectious agents. This percentage was even higher in less developed regions (22.9%) in comparison with more developed ones (7.4%).[8] The International Agency for Research on Cancer Monographs considered Infection as a significant contributor to cancer development and identified eleven biological agents as group 1 carcinogens, however Mtb was not included.[9,10]

The coexistence of pulmonary Tb and lung cancer is not an uncommon clinical observation.[11] There are several studies that have attempted to reveal the exact relationship between Tb and LC.[11-20] Some of their findings are summarized in table I. A prospective study evaluating the association between a history of respiratory diseases (asthma, chronic obstructive pulmonary disease [COPD], Tb) and the development of LC found that there was no relationship between Tb infection and the development of lung cancer. The study does not take in account for confounding factors.

Table I
EPIDEMIOLOGIC REPORTS LINKING LUNG CANCER AND TUBERCULOSIS INFECTION

Author	*Country*	*Study Design*	*Num. Subjects*	*Findings*
Engels *et al.* (2009)[19]	China	Retrospective cohort study	42 422	LC HR (95%CIs) was 9.7 in the first five years after Tb diagnosis.
Yu *et al.* (2011)[20]	Taiwan	Prospective longitudinal study	716 827	LC HR (95%CIs) was 4.37 in the Tb cohort.
Liang *et al.* (2009)[11]	Medline, PubMed, Embase and the China National Knowledge Infrastructure	Meta-analysis	137 334	LC RR was 1.74 (95%CIs) in the Tb cohort and remains 2-fold higher over the 20 years following a Tb diagnosis.
Wu *et al.* (2011)[14]	Taiwan	Retrospective cohort study	29 641	LC HR (95%CIs) was 1.64 in the Tb cohort.
Brener *et al.* (2011)[17]	North America, Asia and Europe	Meta-analysis	82 716	LC RR was 1.74 (95%CIs) in the Tb cohort.
Zheng *et al.* (1987)[15]	Shanghai	Prospective longitudinal study	2 900	LC OR (95%CIs) was 1.5 in the Tb cohort and remains 2.5-fold higher over the 20 years following a Tb diagnosis.
Shiels *et al.* (2011)[16]	North America	Prospective longitudinal study	29 133	LC HR (95%CIs) was 1.97 in the Tb cohort.
Littman *et al.* (2004)[13]	North America	Prospective longitudinal study	17 698	No correlation
R. Everatt *et al.* (2016)[18]	Lithuania	Retrospective cohort study	21 986	No correlation

LC: Lung Cancer, Tb: Tuberculosis, OR: Odds Ratio, RR: Relative Risk, HR: Hazard Ratio

The participants of the study came from the Carotene and Retinol Efficacy Trial (CARET), a randomized, double-blind, placebo-controlled prevention trial with a eligibility criteria that includes two high-risk groups: heavy smokers and asbestos-exposed workers.[13] Everatt and colleagues examined the risk of LC in a Lithuanian cohort of 21 968 Tb patients and took in to account for different confounding factors. They observed a more than three-fold increase risk of lung cancer in individuals with a history of Tb, but the risk declined substantially >3 years after Tb diagnosis in non-smokers therefore concluding that most of the observed risk possibly reflects the confounding effects of reverse causation, closer medical surveillance and shared risk factors.[18] In contrast, in a cohort study in a rural population in China that included 42 422 subjects, reported that the risk of LC increases up to eight times in patients who have a history of Tb infection (25 vs 3.1 per 10 000 person-year). The adjustment for confounding factors such as demographic characteristics, lung disease, and tobacco consumption did not affect the results.[19]

Other reports with an experimental design in Asian population, successfully demonstrated that there is an increased risk of developing LC after Tb infection. Yu and colleagues conducted a prospective cohort study with 716 872 individuals and the results from this study showed that the incidence of LC in patients with Tb is approximately 11 fold higher (26.3 vs 2.41 per 10 000 person-years). Worth mentioning are the hazard ratios of other risk factors that were further increased in the presence of a positive history of Tb infection, such as COPD and Tb (HR 6.22 (95%CI: 4.87-7.94) and smoking and Tb (HR 15.5 (95%CI: 2.17-110).[20] Furthermore, a recent meta-analysis that included 41 studies (37 case-control and four cohort studies) and was adjusted for confounding factors such as passive and active smoking, reported that the risk of developing LC was increased among patients with a history of Tb (2-fold higher over the 20 years following a Tb diagnosis). Interestingly, the histological subtype of LC more frequently associated with a history of Tb was adenocarcinoma (RR 1.6, 95%CI: 1.2-2.1), while the other histological types (squamous and small cells carcinomas) did not show significant association with Tb.[11] It is important to note that having a history of Tb not only increases the risk of developing LC, but it can also negatively affect the prognosis of LC patients. In a cohort study conducted in the Netherlands with about 8 000 subjects and a follow-up of 18 years, a total of 214 cases of LC were found, of which 13 had a history of Tb. The overall survival of patients with LC and a history of Tb was lower compared to those without a history of Tb (HR = 2.36, 95%CI: 1.1-4.9), with an average difference in results between the two groups of 311 days (10 months).[21]

Mechanism of MTb infection

Host macrophages (MQ) are the first ones to encounter MTb following the inhalation into the alveolar spaces. During this first stage, MQ will phagocyte the bacteria that may be exposed to toxic agents such as reactive oxygen species (ROS) and nitric oxide (NO). Afterwards, the bacterium will reside within the phagosome, where they are exposed to more cytotoxic factors such as lysosomal hydrolases, antimicrobial peptides and glutathione.[22] Meanwhile, this encounter also triggers the production of cytokines and chemokines by the MQ, which play pivotal roles in the induction of innate immunity, adaptive immunity and apoptosis. MTb is capable of blocking phago-lysosomal fusion and acidification, partially inhibiting the activation of MQ by Interferon Gamma (INF-γ) a major effector of the Th1 CD4 cell response.[23] The result is bacterial killing and the persistence of some mycobacteria, leading to chronic antigenic stimulation and T-cell accumulation around MQ. The close apposition of MQ and lymphocytes is necessary to activate more MQ that will try to kill MTb. Thus, these cells congregate producing nodular structures called granulomas. The beginning of the granuloma takes part when MQ differentiate into epithelioid cells or activated MQ; some of them fuse forming giant cells. Within the resulting granuloma, there is a balance between killing and survival of MTb that leads to latent Tb infection. This process controls the infection in 95% of subjects, while the remainder progress to active Tb disease. It is estimated that 5-7% of the two billion subjects with latent Tb will have reactivation of the infection, and almost 30% of them will be co-infected with HIV.[23,24]

Chronic inflammation and cancer

The pathophysiological mechanisms of this relationship have not been fully elucidated. However, there is vast preclinical and clinical evidence suggesting that strong and chronic inflammatory responses promote cancer development and progression through different mechanisms. Some hypothesis link lung epithelium DNA damage with the involvement of both free-radical-induced DNA damage and the maintenance of a pro-inflammatory and immunosuppressive cytokine network.[25,26]

In granulomas during active Tb, the intense inflammatory response against mycobacteria has the ability to generate tissue damage. Respiratory symptoms can

last months before clinical diagnosis and treatment entails at least 6-9 months of multidrug treatment. During this extended time, it has been shown that MTb induces the release of inflammatory mediators such as tumor necrosis factor (TNF), INF-γ, IL-1, IL-2 and IL-12 causing inflammation of lung tissue,[27,28] framing how inflammation might be conceived to be a cancer initiator or promoter. In addition, the tissue repair process characterized by high activity levels of fibroblasts, which synthesize extra-cellular matrix (ECM) components and eventually produce fibrosis, that may also be involved in the development of LC, related to the production of TGF-β, IL-4, IL-10, IL-3 and IL-13.[26-28] The role that scarring may play in the pathogenesis of the neoplastic process is obscure; Tb-induced scars have been hypothesized to play an etiologic part in lung cancer for more than 70 years.[11,29] Tissue repair is associated with cellular proliferation, during which errors in chromosomal replication might lead to further DNA mutations. Some pro-inflammatory cytokines, such as TNF and IL-6, may also act directly on epithelial cells to up regulate the expression of anti-apoptotic genes through the NF-kB pathway.[27] Moreover, angiogenesis, the process of new blood vessel formation is a common feature of tissue repair and is also crucial for tumor growth. By creating an environment conducive to DNA mutation, cellular proliferation and angiogenesis, inflammation may thus initiate or promote cancer development.[30]

Gene transfer as a mechanism of neoplastic transformation

Lateral gene transfer (LGT) occurs most frequently between bacteria and their eukaryotic endosymbionts. Many pathogens, particularly viruses, promote cancer through well-described genetic disruption mechanisms,[31] but the only bacteria classified as a biological agent in the group 1 carcinogen is *Helicobacter pylori* which promotes the development of gastric cancer through epithelial injury and inflammation.[32-34] LGT is less common in mammals but in vitro experiments demonstrated that *Bartonella henselae* and *Bartonella quintana* are able to integrate their plasmid DNA into the human genome, making them one the few bacteria that could cause tumor formation in humans.[35,36] Riley and colleagues performed a bioinformatic analysis of the nuclear and mitochondrial genome in normal and tumor tissue from public available sequence data. They found frequent incidences of LGT involving *Acinetobacter*- and *Pseudomonas*-like DNA integrated via RNA intermediates in the human genomes from samples of acute myeloid leukemia with a higher rate of integration in cancer cells being more frequently integrated in the mitochondrial genome than in the nuclear genome. The cancer samples had a 210-fold higher frequency of integration of bacterial DNA than the normal tissue.[37] Taking this in account and considering that mycobacteria is an intracellular bacteria, it will be interesting to explore if MTb can play an active role in the cellular transformation that promotes LC by LGT. In fact, we have recently found through DNA massive sequencing in some cases of adenocarcinoma, diverse mycobacterial genes integrated in the DNA of neoplastic cells (unpublished results).

EGFR mutations and their relation with tuberculosis

Improved treatment has been achieved with the development of targeted drugs for patients with actionable mutations.[38,39] For instance, Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKIs) are superior to chemotherapy in terms of objective response rate (ORR), progression free survival (PFS) and quality of life. The median overall survival (OS) for patients with advanced-stage NSCLC treated with TKIs is approximately 12 months and up to 18 months for patients with adenocarcinoma. It has been found that 70% of patients with increased response to TKI treatment harbour somatic EGFR gene mutations in the kinase domain.[40] The most common EGFR mutations in patients with NSCLC include short in-frame deletions in exon 19 (Del19) and a specific point mutation in exon 21 at codon 858 (L858R).[41]

Reports regarding the impact on the incidence and the outcome of patients with a history of Tb with LC and EGFR mutations are scarce. A report from Taiwan observed a higher incidence (OR: 1.83 [0.92-3.62]) of EGFR mutations in patients with lung adenocarcinoma who had radiographic evidence compatible with old Tb pulmonary lesions.[42] Another retrospective study that analyzed the National Health Insurance Research Database of Taiwan, included 8 265 patients with LC who received EGFR-TKIs between 1996 and 2000 reported that a history of pulmonary Tb is associated with poor clinical response to EGFR-TKIs in male patients but better response in female patients.[43] Tb is one of the most common chronic pulmonary infections leading to chronic inflammation, which has been related to EGFR mutation. Some examples are Nitric oxide-induced (iNOS) EGFR-dependent phosphorylation in A431 tumor cells[44] or the increased expression of epiregulin in invasive EGFR-mutant cells with high invasive properties[45] have been reported before, both (iNOS and epiregulin) of them showed an increased expression during the

course of chronic inflammation in animal models.[43,46] These observations suggested the existence of a relationship between pulmonary Tb and EGFR mutations in patients with lung adenocarcinoma. However, the detailed pathophysiology remains to be studied.

Conclusions

The epidemiological association between Tb infection and LC is well documented. Nevertheless, the molecular mechanisms by which TB promotes the development and progression of LC remains unknown.

The main hypothesis for the association between LC and Tb suggests strong and chronic inflammatory responses during the chronic infection, promote cancer development and progression creating an environment favorable to DNA mutation, cellular proliferation and angiogenesis. Furthermore, there is evidence describing how MTb is capable of partially inhibiting the activation of the immune response on its favor,[23] therefore, it is not unreasonable to explore the new hypothesis where MTb participates actively in the cellular transformation that leads to cancer. Many pathogens promote cancer through well-described genetic disruption mechanisms like LGT, and there is increasing evidence of the presence of genetic material in different types of cancer.[35-37] Further work will uncover the mechanistic relationship between Tb and LC, and will determine the relevance of the possible active participation of MTb in the development of LC.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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