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Review Article

Effects of Mycobacterium tuberculosis infection on the lungs and the immune system: an integrative review*

Efeitos da infecção por Mycobacterium tuberculosis no pulmão e no sistema imune: uma revisão integrativa

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ABSTRACT: Introduction: Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (Mtb), a strictly aerobic, non-encapsulated, and non-sporulating bacillus. **Objective:** To gather effects of Mtb infection of lungs and the immune system. **Method:** An integrative review was conducted between May and June 2023, using PubMed database with the following search strategies: "*Tuberculosis, Pulmonary*" *AND Necrosis*; "*Mycobacterium tuberculosis*" *AND "lung injury*"; "*Mycobacterium tuberculosis*" *AND* "*immune system*" *AND Inflammation*. Original articles published between 2018 and 2023 that met the review's objective were selected. **Results:** A total of 134 articles were obtained from the search, 126 were excluded after reading the title, abstract, and full text, remaining 8 articles selected to compose this review. The studies indicated that Mtb infection stimulates the production of cytokines such as TNF-α, IFN-γ, and IL-10, inducing variations in their serum levels depending on the stage of the disease and the spread of infection. Additionally, there were changes in the rates of B lymphocyte growth factors and the production of anti-TB antibodies, leading to the formation of granulomas and macroscopic lung lesions. **Conclusion:** The effects of Mtb infection on the lung and the immune system are inferred to be instigated by the action of various cytokines, which will modulate the inflammatory and immune response against the bacterium.

KEY WORDS: Inflammation; *Mycobacterium tuberculosis;* Lung; Immune System; Tuberculosis.

RESUMO: Introdução: Tuberculose (TB) é uma doença infectocontagiosa causada pela bactéria *Mycobacterium tuberculosis* (Mtb), um bacilo aeróbio estrito, não encapsulado e não esporulado. **Objetivo:** Compilar os efeitos da infecção por Mtb no pulmão e no sistema imune. **Método:** Revisão integrativa realizada entre maio e junho de 2023, na base de dados PubMed, com as seguintes estratégias de busca: "*Tuberculosis*, *Pulmonary*" *AND Necrosis*; "*Mycobacterium tuberculosis*" *AND* "*lung injury*"; "*Mycobacterium tuberculosis*" *AND* "*immune system*" *AND Inflammation*. Foram selecionados artigos originais publicados entre 2018 e 2023 que atendessem ao objetivo desta revisão. **Resultados:** Obteve-se um total de 134 artigos com a busca, dos quais foram excluídos 126 após leitura do título, do resumo e da leitura na íntegra, restando 8 artigos selecionados para compor esta revisão. Os estudos indicaram que a infecção por Mtb estimula a produção de citocinas, como TNF-α, IFN-γ e IL-10, e induz variações em seus níveis séricos conforme o estágio da doença e disseminação da infecção, além de alterações nas taxas de fatores de crescimento de linfócitos B e na produção de anticorpos anti-TB, formando granulomas e lesões macroscópicas pulmonares. **Conclusão:** Depreende-se que os efeitos da infecção por Mtb no pulmão e no sistema imune são instigados pela ação de diversas citocinas, que irão modular a resposta inflamatória e imune contra a bactéria.

PALAVRAS-CHAVE: Inflamação; *Mycobacterium tuberculosis;* Pulmão; Sistema Imunitário; Tuberculose.

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (Mtb). It is estimated that the first cases of tuberculosis in Brazil occurred during Portuguese colonization in 1549[1]. Although there were several cases of tuberculosis, it was not until 1882 that the physician Heinrich Hermann Robert Koch proved the idea that TB was caused exclusively by the bacillus of the genus Mycobacterium and that its transmission occurred with the elimination of the bacterium from the body through sneezing, saliva droplets and phlegm[2]. In addition, it is noteworthy that the bacterium is more prevalent in individuals in situations of extreme vulnerability - low levels of income, education and inadequate housing - that, in the absence of adequate health coverage, there is an increase in the spread of the disease[3].

Mtb is a strict, non-encapsulated, non-spore-forming aerobic bacillus that retains basic fuchsin in its cell wall, even in the presence of alcohol and acid - a fact that characterizes it as an acid-fast bacillus (AFB) - and that proliferates inside macrophages[4]. The action of Mtb in the body begins, most of the time, through the inhalational route, in which the nasal cilia, the cough reflex and mucociliary clearance try to eliminate the bacilli by physical mechanisms and, if this is not possible, the bacterium settles. After about three to four weeks, the pulmonary focus begins[5].

Upon reaching the lungs, Mtb will be phagocytosed by type II pneumocytes and alveolar macrophages, which release chemokines that attract and activate neutrophils, monocytes, lymphocytes and other inflammatory cells that conjugate to destroy them[5]. Although alone they are not efficient in fighting the bacterium, the joint action with tumor necrosis factor-alpha (TNF-α), which induces reactive nitrogen intermediates (RNI) and caseous necrosis, and interferon gamma (IFN-γ), make the medium lethal for BK[3]. In this context, the influence of CD4+ T lymphocytes can be perceived, in which their TH1 subgroup inhibits BK growth by regulating the immune response. It is from the T lymphocytes that the granulomatous lesion characteristic of TB begins, through the formation of a granuloma, which contains epithelioid cells and Langerhans giant cells and, in its envelope, CD4+ and CD8+ T lymphocytes[5]. Therefore, with the development of cellular immunity, this center of the granuloma undergoes a process of caseous necrosis, which can also be induced by BK, through TNF-α and lipoarabinomannan glycoprotein (LAM), which is present on the surface of the bacillus that mediates the interaction between mannose receptors and BK[5].

Thus, the pathophysiogenesis of TB is characterized in the primary phase as asymptomatic and mild, with a Ghon's lesion, a calcified nodule, and, as the disease progresses, patients develop daytime fever, night sweats, weight loss, anorexia, malaise, weakness, and cough with occasional massive hemoptysis[4]. Therefore, TB is treated with antibiotics, such as rifampicin, isoniazid, pyrazinamide, and ethambutol[6], and one of the forms of prevention is through the BCG vaccine[2].

There is a high incidence of tuberculosis in Brazil, with 66,796 new cases reported in 2016 and 12,809 in retreatment, with the highest prevalence in illiterate patients aged 30-39 years[3]. Also in 2019, 73,864 new cases were registered with the occurrence of 6,700 deaths, which corresponds to a mortality coefficient of 3.17 deaths per 100 thousand inhabitants. It is worth noting that the Notifiable Diseases Information System (SINAN) records only after the diagnosis is confirmed, made through clinical history, chest X-ray, chest computed tomography, bronchoscopy, tuberculin skin test, or Mantoux reaction[7,8].

When looking at the epidemiological data of TB in Brazil from 2018 to 2022, the severity of the disease is noted, since 470,915 cases were reported[7], and one person is capable of infecting about 10 to 15 other individuals per year in the country[2]. It was observed that during the Covid-19 pandemic, there was a decrease in TB cases, which can be justified by the increased use of masks, hand hygiene, and distancing. Another relevant factor was that infected patients develop neutralizing antibodies after 2-4 weeks, which help fight TB[9]. Therefore, it is essential to approach this topic in order to understand how Mtb acts on the immune system and its form of contagion. Therefore, this study aims to compile the effects of Mycobacterium tuberculosis infection on the lung and immune system.

METHODS

This is a literature review following an integrative methodology[10]. The following guiding question was used to guide the conduction of the review: "What are the effects caused by Mtb infection on the lung and the immune system?". The descriptors "Tuberculosis, Pulmonary", Necrosis, "*Mycobacterium tuberculosis"*, "Lung injury", "Immune system" and Inflammation, extracted from the Health Sciences Descriptors (DeCS/MeSH) database, were used to formulate the three search strategies used in the PubMed database, between May and June 2023. "Tuberculosis, Pulmonary" AND Necrosis; *"Mycobacterium tuberculosis*" AND "lung injury"; "Mycobacterium tuberculosis" AND "immune system" AND Inflammation. The criteria used to include the articles in the review were: published between 2018 and 2023; written in English or Portuguese; be available in full. Articles that did not answer the guiding question, meta-analyses, and other literature reviews were excluded from the review. The criteria were employed by two different researchers, who selected the articles first by reading the title and abstract and then by reading the article in its entirety. A complementary manual search was performed in order to add new articles, obtained from other databases and without applying the same criteria, in order to improve the discussion of the results.

RESULTS

By using the three search strategies described in the method and after applying the filters, a total of 134 articles were found. After excluding articles by reading the title and abstracts, 13 articles were obtained, which were read in full, and thus, another five articles were excluded because they did not deal with the theme of this review, totaling the inclusion of 9 articles, which are shown in Table 1.

Table 1 - Studies included in the review and their background information.

Study	Title	Authorship	Year
1	*Altered circulating levels of B cell growth factors and their modulation upon antituberculosis treatment in pulmonary tuberculosis and tuberculous lymphadenitis*	KATHAMUTHU *et al.*	2018
2	*Sex influences the association between haemostasis and the extent of lung lesions in tuberculosis*	TAN *et al.*	2018
3	*Immunological host responses as surveillance and prognostic markers in tubercular infections*	WAGHMARE *et al.*	2019
4	*Mycobacterium tuberculosis exploits focal adhesion kinase to induce necrotic cell death and inhibit reactive oxygen species production*	AFRIYIE-ASANTE *et al.*	2021
5	*Mycobacterium tuberculosis load in host cells and the antibacterial activity of alveolar macrophages are linked and differentially regulated in various lung lesions of patients with pulmonary tuberculosis*	UFIMTSEVA *et al.*	2021
6	*Autoantibodies to tumor necrosis factor in patients with active pulmonary tuberculosis*	KIREEV *et al.*	2022
7	*Changes of Th1 and Th2 cytokines levels among sudanese tuberculosis patients during treatment*	ABDUL-AZIZ *et al.*	2022
8	*Pathology of pulmonary tuberculosis: has the tiger changed it's stripes?*	DESAI *et al.*	2022
9	*B cells promote granulomatous inflammation during chronic Mycobacterium tuberculosis infection in mice*	CHEN *et al.*	2023

Source: Prepared by the authors (2023)

TNF plays an important role in the immune response to TB, the main one being to ensure the latency of bacterial infection. Kireev *et al*., based on blood collection from 45 patients with TB and 150 without TB, analyzed the serological levels of TNF and anti-TNF autoantibody by means of enzyme-linked immunosorbent assays (ELISA). Their study found similar levels of TNF between TB patients and healthy individuals. However, when comparing TNF levels among TB patients, it was found that disseminated infection (infection occupying more than two segments) is linked to a higher TNF value than localized infection (infection occupying one or two segments). Patients with more severe manifestations, with the pathogen isolated by bronchoscopy, also demonstrated higher levels of TNF. Regarding the titration of serum levels of the anti-TNF autoantibody, the IgG class showed significantly higher levels in TB patients than in healthy patients, unlike immunoglobulin M (IgM) and immunoglobulin A (IgA). The immunoglobulin G3 (IgG3) subclass was elevated in tuberculosis patients when compared to healthy individuals, while immunoglobulin G1 (IgG1) and immunoglobulin G2 (IgG2) remained stable. Among patients with disseminated infection in whom Mtb was isolated by bronchoscopy, IgG, IgG1 and IgA levels were elevated[11].

The retrospective study by Desai *et al.* described macroscopic and microscopic patterns and Ziehl-Neelsen staining and TB complications. Over a three-year period, 130 autopsies of patients who died after TB infection were conducted. Among the macroscopic morphological alterations, non-cavitation bronchopneumonia was the most present in 47 of the cases (36.15%), followed by miliary lesions in 34 cases (26.15%), nodular lesions in 19 cases (14.62%) and fibrocavitary lesions in 17 cases (12.08%), bronchopneumonia with cavitation in 12 cases (9.23%), and pleuritis in only one case (0.77%). In addition, TB complications were analyzed, including vasculitis, in 55 cases (42%), observed with bronchopneumonia, in 16 cases, diffuse alveolar hemorrhage, three cases (2.3%), diffuse alveolar damage, 11 cases (8.4%), and pulmonary thromboembolism, two cases (1.5%)[12].

Blood samples from 145 individuals, including 85 patients with recent TB (58.6%), 25 in follow-up with TB (17.2%), and 35 in a healthy control group (24.1%), measured plasma levels of the cytokines interleukin 10 (IL-10), TNF-α, and IFN-γ in the study by Abdul-Aziz *et al*. The diagnosis of the disease was made based on Ziehl-Neelsen staining (for recent disease) and PCR test (for disease under follow-up). In patients with new TB cases, serological IFN-γ levels were significantly higher than in the healthy control group and the follow-up group. No significant differences were found between IL-10 and TNF-α in patients with recent TB, healthy control group, and ongoing TB[13].

The research by Kathamuthu *et al*. examined the magnitude of the importance of proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF) as B-type lymphoid cell growth factors in patients with active pulmonary tuberculosis (PTB), latent tuberculosis infection (LTL), tuberculous lymphadenitis (LTB), and in a healthy control group (CH), each of the groups with 44 individuals. APRIL was found to be significantly reduced in PTB patients relative to the other three clusters, with 130.1 pg/mL in PTB, 2859 pg/mL in LTL, 2582 pg/mL in LTB, and 2582 pg/mL in HC. On the other hand, circulating levels of BAFF were found to be elevated in PTB and

LTB, with 571.7 pg/mL and 795.9 pg/mL, respectively, when compared with LTB (290.7 pg/mL) and CH (283.2 pg/mL). The study also revealed decreases in the levels of APRIL and BAFF after the treatment of PTB, in which titrations were found, which went from 130.1 pg/mL to 121.8 pg/mL and from 571.7 pg/mL to 274.5 pg/mL, respectively[14].

Tan *et al.,* Using 114 pairs of female and male patients with primary pulmonary tuberculosis, we compared the number of patients with TB in lung lesions, sputum, and antibodies. The analysis was performed using T-SPOT kits. TB and ELISA kits to detect serum anti-TB and T-SPOT IgG antibody levels. TB. Bacteria were observed in the sputum in 46.5% of the male patients and in 25.6% of the female patients, but there was no difference between the sexes in relation to the positive response in both the anti-TB antibody and the T-SPOT test. TB. When evaluating differential lung lesions, it was found that men had greater lung damage, with more cavitary lesions (70.5% versus 37.2%, $P < 0.001$) associated with emphysema-scarring, pleural thickening, bronchovascular distortion, and parenchymal bands. In addition, regardless of gender and age, low lymphocyte counts were related to higher sputum bacterial counts[15].

Blood samples were collected from patients with TB relapse (group 1), newly diagnosed (group 2), undergoing antituberculosis [RTA] treatment (group 3) and healthy controls (group 4) to assess the level of serum cytokines and chemokines in the study by Waghmare *et al*. The study revealed low means of TNF-α and IFN-gamma in the group treated with RTA - with the exception of one individual who had high levels of TNF-α (102.36 pg/ml) - and values in patients with TB relapse. The cytokine IL-10 showed a significant difference between almost all groups, except between groups 1 and 2, where it remained at low levels. In addition, when comparing the groups and the Bonferroni test, a significant difference in TNF-α was revealed between all groups, with low mean levels in group 3 and high levels in the group with relapsed TB and IL-10 with a difference between groups 2 and 3[16].

The study by Afriyie-Asante *et al*. evaluated the influence of Mtb infection on the expression of Focal Adhesion Kinase (FAK), from a line of human THP-1 macrophages/monocytes with an mc 26206 strain of Mtb H37Rv. In the analysis carried out over four days, it was observed that the total levels of FAK decreased during infection (reached approximately 25% compared to wild-type control cells) and that this reduction is related to the The level of mRNA transcription of PTK2 (the gene encoding FAK) was increased, as it decreased in a similar way during infection. To assess how FAK influences the antibacterial response of macrophages, THP-1 cells were genetically modified to overexpress FAK, and as a result, there was a protein reduction of 17% - 37% relative to uninfected FAK+ macrophages. Regarding the study of the effect of FAK expression on the production of cytokines by THP-1, THP-FAKi and THAP-FAK+ macrophages, due to Mtb infection, it was observed that pro-inflammatory cytokines (TNF-α and IL-1β) are found in significantly lower numbers in THP-FAK+ and in greater quantities in THP-1 and THP-FAKi macrophages. In contrast, basal levels below the IL-10 threshold were observed in the three strains, which is in line with the increase in IL-10 production during FAK overexpression, i.e., there is a reduction in inflammation with increasing levels of FAK and an increase when there is protein inhibition. To determine whether FAK regulates a necrotic form of cell death, the Lactate Dehydrogenase (LDH) assay, an enzyme that indicates tissue injury, was used, and an increase in LDH release during FAK inhibition and a decrease in LDH during FAK overexpression were revealed. When performing a pyroptosis induction by inflammosome activation using LPS and nigericin, there was no difference in IL-1β production, however, chemical induction of pyroptosis revealed an increased IL-1β production. THP-1 macrophages were infected with luciferase-expressing Mtb for 6 days and the bacillary load was quantified, with an exacerbated replication of Mtb during FAK inhibition and a time-dependent reduction of bacillary load during FAK overexpression compared to THP-1 macrophages[17].

To evaluate the ex vivo production of cells, Ufimtseva *et al.* recruited eight patients with pulmonary tuberculosis and, after prolonged antibiotic therapy, underwent surgery to remove lung parts of the tuberculoma walls. In the macroscopic evaluation, small necrotic nodules with fibrotic encapsulation with a diameter of up to 5 mm were observed in both tissues. The Ziehl-Neelsen histological examination revealed a large central region of caseous necrosis, surrounded by a thick and dense fibrotic border with a large amount of fibroblasts and collagen, as well as scattered alveolar macrophages and a small amount of multinucleated Langerhans giant cells and pneumocytes. Ex-vivo cell cultures were isolated from the tuberculoma walls to determine the number of Mtb-infected cells; in the 18th hour, almost the total number of cells from different lung lesions (87%-100%). They were composed of viable alveolar macrophages without apoptotic and necrotic morphology, however, most of these macrophages, in both specimens, had a large number of dark inclusions in the cytoplasm. In addition, in this study, the biosynthesis of Reactive Oxygen Species (ROS) in alveolar macrophages after ex vivo culture for 18 hours was also examined, and by means of immunofluorescence of histological sections and ex vivo cell culture, the expression of inducible Nitric Oxide Synthase (iNOS) and Cyclooxygenase 2 (COX-2) in the cells was evaluated. It was revealed that these compounds were found in vesicles of different sizes in the cytoplasm of the positive markers and, in ex vivo cell culture, the expression of iNOS was mainly associated with the plasma membrane of the positive alveolar macrophages. Only single Mtb was observed in the necrotic areas of the tuberculomas, i.e., the higher Mtb load was related to the decrease in the pro-inflammatory activity of the tuberculomas.[18].

The study by Chen *et al.* demonstrated the importance of B lymphocytes in pulmonary inflammation in chronic tuberculosis. Using mice, the role of these cells in modulating the inflammatory response and the effects of their deficiency were studied. It was found, in a histological analysis produced by the researchers, that in chronic tuberculosis the deficiency of B cells (μMT) is related to the decrease of the granulomatous inflammatory response. In addition, rats with this deficiency, when induced to inoculate Mtb, survived longer than normal rats (from 272 days to 324, on average). The study also indicated that the lower amount of Mtb infiltrate in the μMT suggests that it is attributed to a lower amount of inflammatory cell expansion in the lungs. In μMT, levels of inflammatory cytokines such as IFN-γ, CD4 T lymphocytes and Th1 response are lower than in control rats. However, this did not restrict the growth of Mtb in the lungs of this group, which remained comparable and with little difference in bacillus load between both groups. The levels of the anti-inflammatory cytokine – IL-10 were increased in the μMT group, related to lower granulomatous inflammation. During the study, the researchers found scarce presence of B cells in areas without necrosis or cavitation – in contrast to regions where these areas were present, in which multiple aggregates of B cells were visible circumscribing the lesions[19].

DISCUSSSION

TB was the cause of 1.6 million deaths in 2021, with approximately 10.6 million new cases in the same year. The incidence of TB fell during the Covid-19 pandemic, while mortality rose during this period, which is different from the global scenario found until 2019[8]. Periods of isolation, the overload of health services, and the failure to diagnose and consequent treatment TB during the pandemic were factors with a strong impact on incidence and mortality. TB has been affected in different ways by the pandemic and continues to be one of the main diseases today. Therefore, we sought to study the relationship of its etiological agent with changes in the lung and immune system.

The pathogenesis of primary tuberculosis – i.e., without prior exposure – is related to the host cell-mediated immune response, with a varied inflammatory response. In the study by Desai *et al*., non-cavitation bronchopneumonia was the most common macroscopic abnormality. This type of injury consists of the consolidation of the lung into foci, due to the accumulation of exudate in the alveoli, compromising gas exchange. The second most common macroscopic alteration was miliary lesions, foci of caseous necrosis of approximately two millimeters in diameter characteristic of hematogenous dissemination. As for microscopic lesions, the absolute majority of patients had caseating granulomas, which are centers of caseous necrosis – identified mainly by the loss of cellular contours – surrounded by activated macrophages, which surround the necrotic focus in an attempt to contain the pathogen during the inflammatory response. Histological findings often include macrophages that fuse to form multinucleated giant cells or whose cytoplasm becomes abundant, generating epithelioid cells. This type of granuloma is responsible for other macroscopic lesion patterns observed in the present study, such as nodular and fibrocavitary lesions[12]. In the latter, connective tissue deposition is observed in the process of post-inflammatory tissue repair with scar formation, in which the injured cells do not recover their functionality[20].

TNF is a pleiotropic cytokine, and its role in regulating the production of certain chemokines can be observed, within its various functions, in order to attract the cells essential for the formation and maintenance of granulomas, and thus contain the focus of infection[21]. Thus, TNF is essential to protect the body both against new Mtb infections and against latent infections by keeping the granuloma active. TNF-α also plays the role of inducing apoptosis of infected cells[22], which is a critical response to reduce the proliferation of the bacterium and to stimulate the development of the adaptive humoral response.

Although TNF-α has several positive effects on the response to TB infection, this cytokine can be a “double-edged sword” in high amounts, since it is responsible for part of the TB pathology and is capable of stimulating the expression of Mtb mRNA in infected monocytes. The bacterium acts by increasing the sensitivity of cells to TNF-α cytotoxicity, leading the cytokine to play an active role in the death of host cells. There are correlations between high levels of TNF-α with greater formation of cavities and areas of caseous necrosis, leading to tissue damage and loss of organ function, in this case of the lung[22]. Thus, it is understood that there is a balance between the effects of TNF on infection control and on TB pathology. According to the analysis of TNF-α levels in groups of patients at different stages of TB performed by Waghmare *et al*., those with relapsing disease showed superiority in the levels of this cytokine[15]. High levels were also observed in cases of recent tuberculosis, but lower than in recurrent cases of the disease, while those who underwent antituberculosis treatment had low levels. On the other hand, Abdul-Aziz *et al.*, when comparing TNF-α levels between recent cases of TB, patients undergoing treatment, and healthy people, did not observe any significant change in TNF-levels between the groups[13]. Both studies indicate a reduction in serum TNF-α levels with antituberculosis treatment, but contradict the levels found in patients with recent tuberculosis. This divergence may be due to the different variables between the groups studied that were not taken into account in the studies, requiring further research and further research.

Kireev *et al.* analyzed TNF levels and described that there were no relevant changes between healthy individuals and those diagnosed with tuberculosis. however, in cases of disseminated tuberculosis (involving more than two lung segments) in which Mtb was isolated on bronchoscopy (Mtb+), elevated TNF levels were observed in comparison with other cases of tuberculosis. These high levels of cytokine serve to explain the greater lung lesions, such as cavity formation, which are characteristic of these more severe cases of pulmonary tuberculosis. Another analysis performed by the study was regarding the serum levels of anti-TNF autoantibodies, finding high levels of IgA, IgG and IgG1 when comparing patients with disseminated Mtb+ tuberculosis with other cases of tuberculosis[11]. These results may indicate a role of these antibodies in the more severe lesions observed in these cases, although there are not yet many studies in this area to prove or deny this hypothesis.

Waghmare *et al.* also analyzed the levels of other cytokines, including IL-10. In the active and relapsed TB groups, levels were low compared to those on treatment or healthy, although the study did not identify large differences between the study populations and their IL-10 levels[16]. This cytokine has different functions in the inflammatory response, in smaller amounts it serves to prevent tissue damage and stimulate the antibacterial response, since it has the ability to inhibit the apoptosis of infected macrophages and the production of Th1 response cytokines, in addition to stimulating the intracellular survival of Mtb23. The role that this cytokine plays is consistent

with its low levels in the active picture of tuberculosis, it can serve as an indicator for the severity of the infection, as well as other cytokines.

IFN-γ acts on both innate and adaptive immunity, regulating phagocytosis, activating defense cells, stimulating the killing of Mtb by neutrophils and macrophages, among other functions[24]. Abdul-Aziz *et al*. found elevated levels of IFN-γ in patients who had recently manifested TB. A decrease in the values of those who underwent treatment was also observed[12], findings that are corroborated by Waghmare et al., who found high levels of the cytokine in cases of tuberculosis recurrence[16]. Thus, the role of IFN-γ in the control of tuberculosis is clear, and its reduction is common after treatment and recovery.

Seeking to analyze the relationship between different stages of tuberculosis and the levels of the cytokines BAFF and APRIL, Kathamuthu *et al*. found high levels of BAFF in cases of active and latent pulmonary tuberculosis and reduced levels in those who underwent treatment. B-cell activating factor plays an essential role in fighting Mtb infection, which is consistent with its reduced levels after treatment and elevated during the immune response. The rates of APRIL in active tuberculosis were significantly decreased compared to the other study populations, which may be explained by the role of APRIL in stimulating BAFF action, thus, low APRIL rates would be a possible cause for the active stage of the disease[14].

Maglione *et al*. observed the role of B cells in the response against Mtb infection, demonstrating that they regulate the production of cytokines and chemokines, controlling the inflammatory response and granuloma formation, although the exact mechanisms by which this happens are still unclear[25]. Thus, B-cell growth factors are essential in modulating this integral part of the immune response against tuberculosis, making it clear why the presence of the bacterium promotes changes in its concentrations.

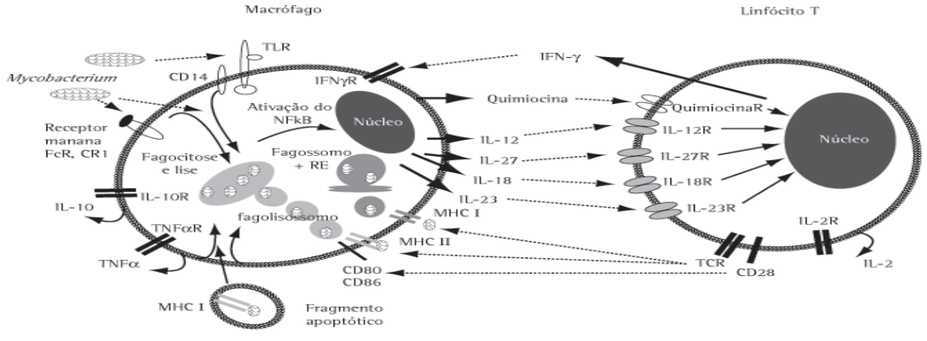
Chen *et al.* also evaluated B lymphocytes in rats, but specifically the inflammatory response in chronic tuberculosis. The study found that the B-cell-deficient mouse line showed a decreased Th1 response, with a consequent reduction in the granulomatous response. The μMT rats survived longer than the control group, which is consistent with the other articles in this review, since there is an absence of an uncontrolled and harmful inflammatory response, and the lesions caused by this exaggerated response caused by the bacillus would occur in smaller quantities[19]. The data also pointed to higher levels of IL-10 in the B-cell-deficient mice, which confirms a role of these cells in inhibiting its production.

Mtb infection leads to the inhibition of FAK in the macrophage, contributing to the lower production of ROS, which participates in the elimination of pathogens by this cell[17]. Thus, the increase in bacillary load demonstrates a mechanism of Mtb survival, inhibiting intracellular phagocytic pathways of macrophages to favor their replication. In fact, the results obtained by Ufimtseva *et al.* corroborate this finding, insofar as they detect a higher bacillary load with a reduction in the inflammatory response after 18 hours in lung lesions, composed of macrophages without apoptotic or necrotic patterns[18].

In addition, the inhibition of FAK is progressive in the course of the inflammatory response. As Ufimtseva *et al.* analyzed pulmonary macrophages 18 hours after infection, they were marked by the expression of iNOS, an enzyme modulated by ROS and which also participates in phagocytic pathways[18]. On the other hand, Afriyie-Asante *et al*. attest to the decrease in ROS and NNOS due to the inhibition of FAK over 4 days, which is more intense after 48 hours of infection[17]. This progressive inhibition of FAK by Mtb favors a pattern of cell death by necrosis, to the detriment of apoptosis. Apoptosis is a programmed cell death pathway, which aims to minimize inflammation, containing cellular debris in apoptotic bodies surrounded by membrane, easily phagocytosed and digested by defense cells. The persistence of cell lesions, in the inactivity of the apoptotic pathways, which are inhibited, leads to a pattern of cell dissolution characteristic of necrosis, leading to the exacerbation of the adjacent inflammatory response. In addition, Mtb acts by necroptosis mechanisms, in which apoptotic signaling elements, such as TNF receptors, and cell dissolution are present, with the participation of receptor interaction proteins (RIP) and pyroptosis, in which chemical agents or cytosolic proteins called inflammatosomes induce an apoptotic response that leads to the release of inflammatory and pyrogenic cytokines[24]. Thus, the inhibition of FAK is related to the worsening of the inflammatory response over time[17].

Figure 1 exemplifies some of the mechanisms related to the immune system's response to Mtb infection, more specifically the action of several cytokines involved in this process[26].

Figure 1 - Mechanism involved in the activation of macrophages and T lymphocytes by mycobacteria.



Source: Teixeira HC, Abramo C, Munk ME (2007).

CONCLUSION

This review synthesized the effects of Mycobacterium tuberculosis infection on the lung and the immune system and showed its link with the action of several cytokines, especially TNF, IL-10 and IFN-γ, which will modulate the inflammatory and immune response against the bacterium. In this sense, it is observed that the formation of areas of caseous necrosis, which leads to tissue loss and lung damage, depends on high levels of these proteins. It is also observed that at the macroscopic level, in the lung tissue, there are small necrotic nodules with fibrotic encapsulation of up to 5 mm, a marked manifestation of TB. At the microscopic level, in the Ziehl-Neelsen histological examination, granulomas, a central region surrounded by a thick border of fibrous tissue, which contains macrophages, fibroblasts, a small amount of Langhans giant cells and the absence of neutrophils, appear. In addition, it is found that the inhibition of FAK in the macrophage promoted by the bacterium results in a lower production of reproductive species.

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